
يوم الأرض العربية

Questions in Dyslipidemias

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المنصورة اليوم
MANSOURA. 2014

When start, start right

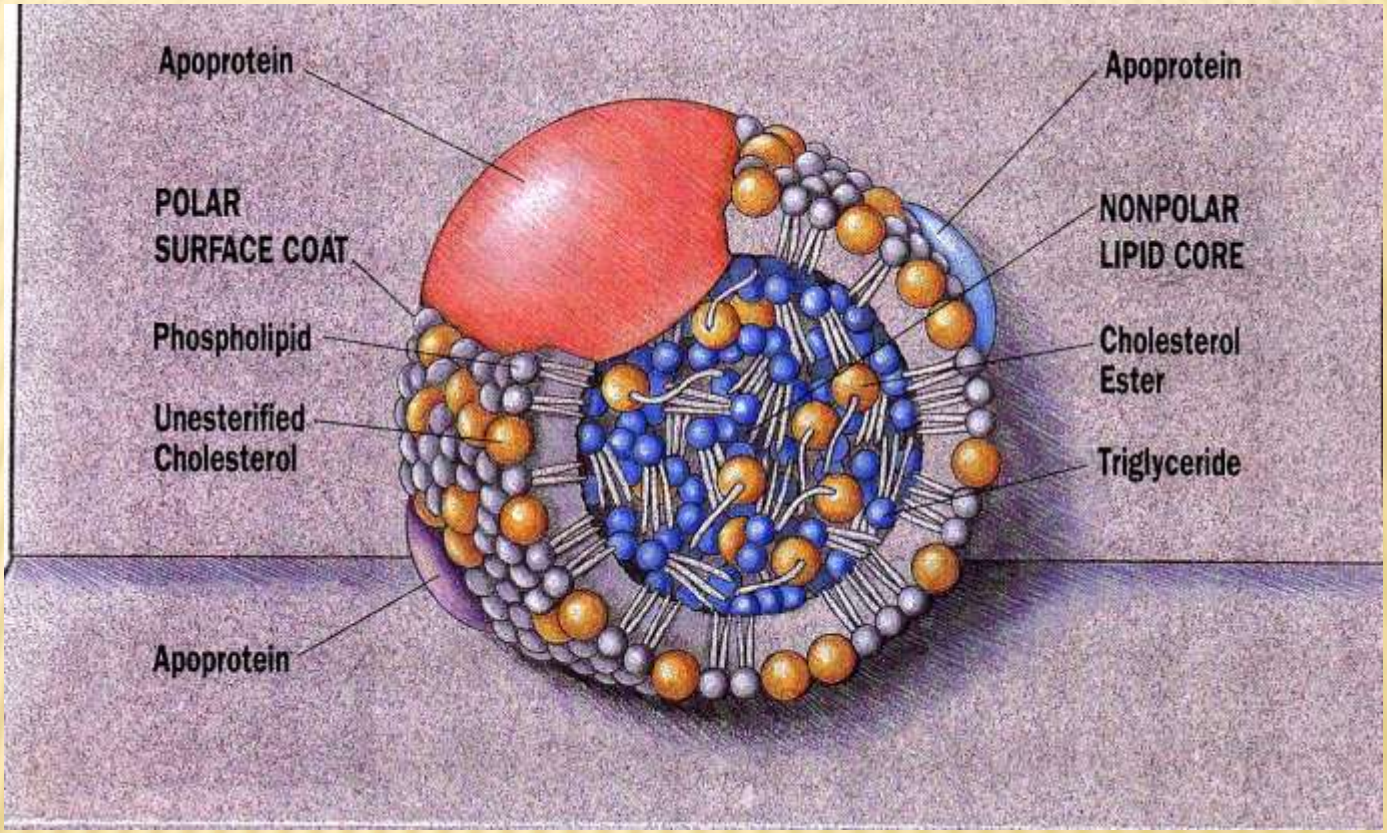
Lipoprotiens?

The lipoproteins :

- **Lipids are water insoluble to be transported through the bloodstream a shell of water-soluble protein and phospholipids pack a core of lipids.**

- **They behave as vehicles transporting cholesterol and triglycerides from one part of the body to another.**

Generic Lipoprotein

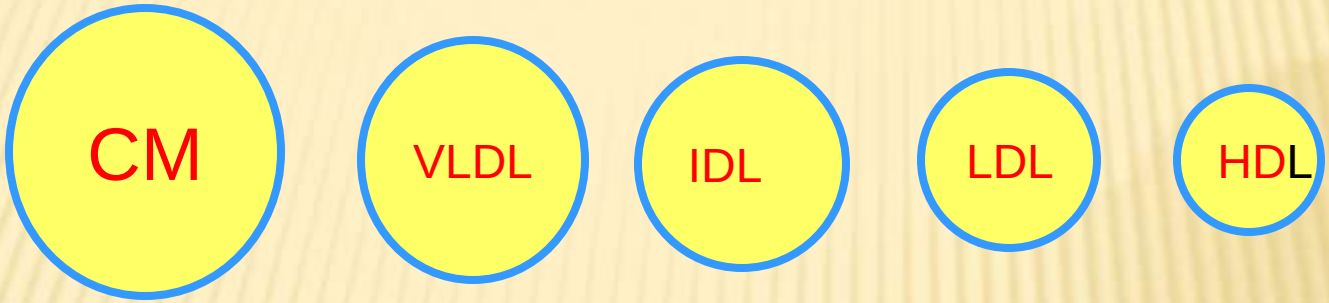


Major lipoproteins in the blood ?

The major lipoproteins in the blood stream :

LIPOPROTEIN	FUNCTION
Chylomicron	Transport diet triglycerides from the gut to adipose tissue and muscle
VLDLs	Trans. endogenous triglycerides from the liver to adipose tissue and Mm
LDLs	Trans. cholesterol from the liver to peripheral tissues
HDLs	Trans. cholesterol from peripheral tissue to the liver

Lipoprotein Nomenclature and Composition

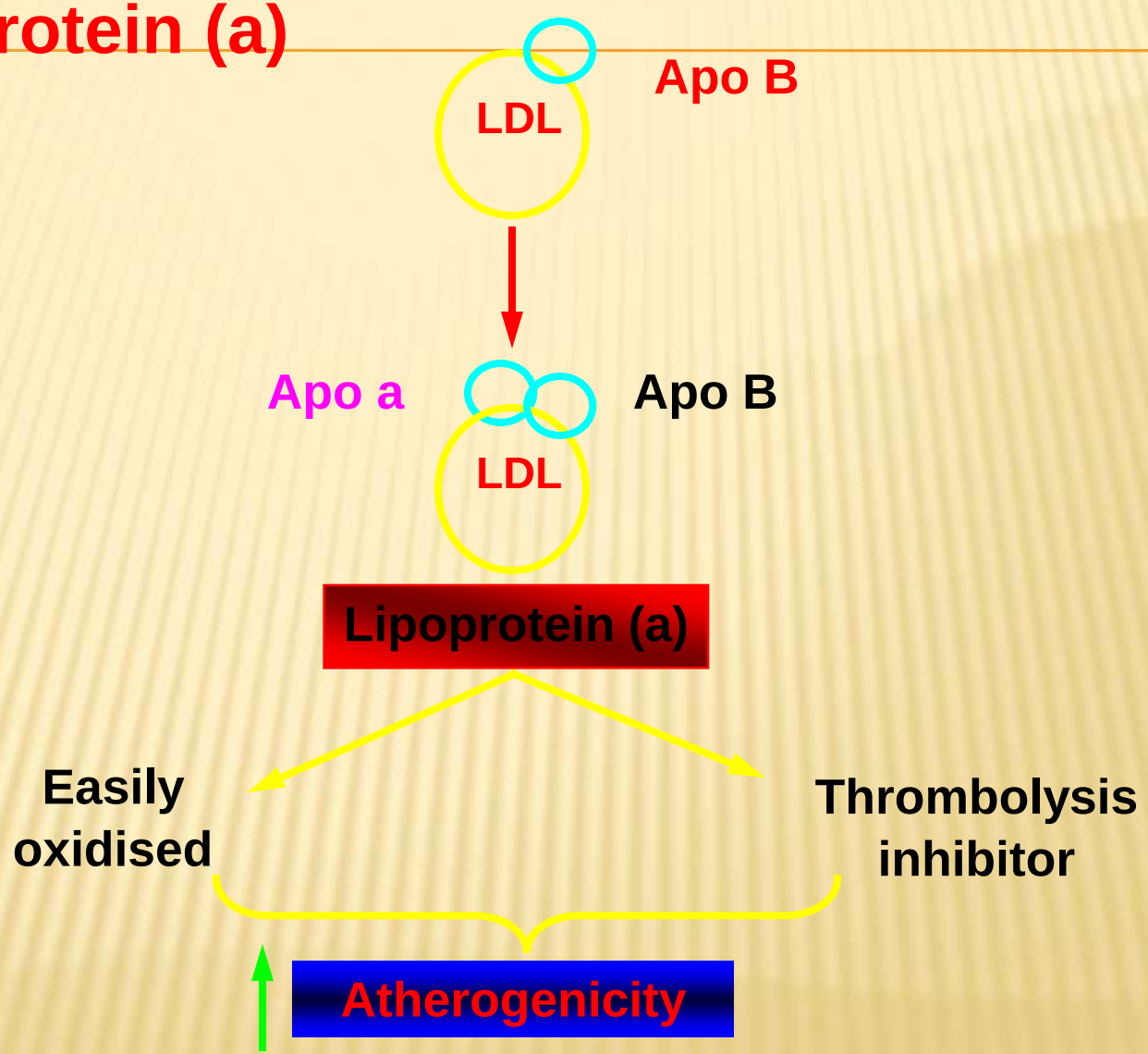


	CM	VLDL	IDL	LDL	HDL
ajor rotein	apoB	apoB	apoB	apoB	apoA-I
ajor Lipid	CE	CE	TG	TG	CE

CM= chylomicron
VLDL= very low density lipoprotein
IDL= intermediate density lipoprotein
LDL= low density lipoprotein
HDL= high density lipoprotein
Apo = apolipoprotein

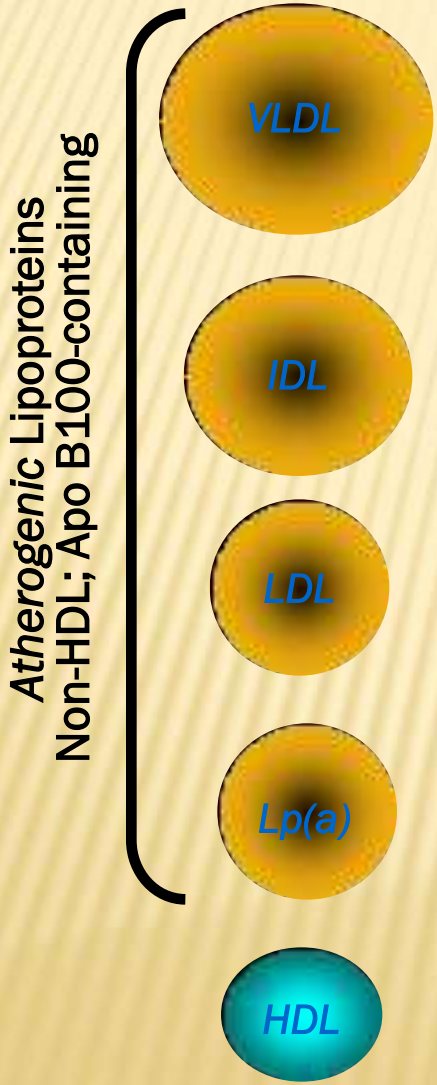
TG=triglyceride
CE= cholesteryl ester

Lipoprotein (a)



NON –HDL?

NON-HDL INCLUDES *ALL* ATHEROGENIC LIPOPROTEIN CLASSES



Very low-density lipoprotein

Made in the liver +
TG >> CE +
Carries lipids from the liver to peripheral tissues +

Intermediate-density lipoprotein

- Formed from VLDL due to loss of TG
- Also known as a VLDL remnant

Low-density lipoprotein

- Formed from IDL due to loss of TG
- CE>>TG

Lipoprotein (a)

- Formed from LDL w/ addition of apo (a)?
- Very atherogenic

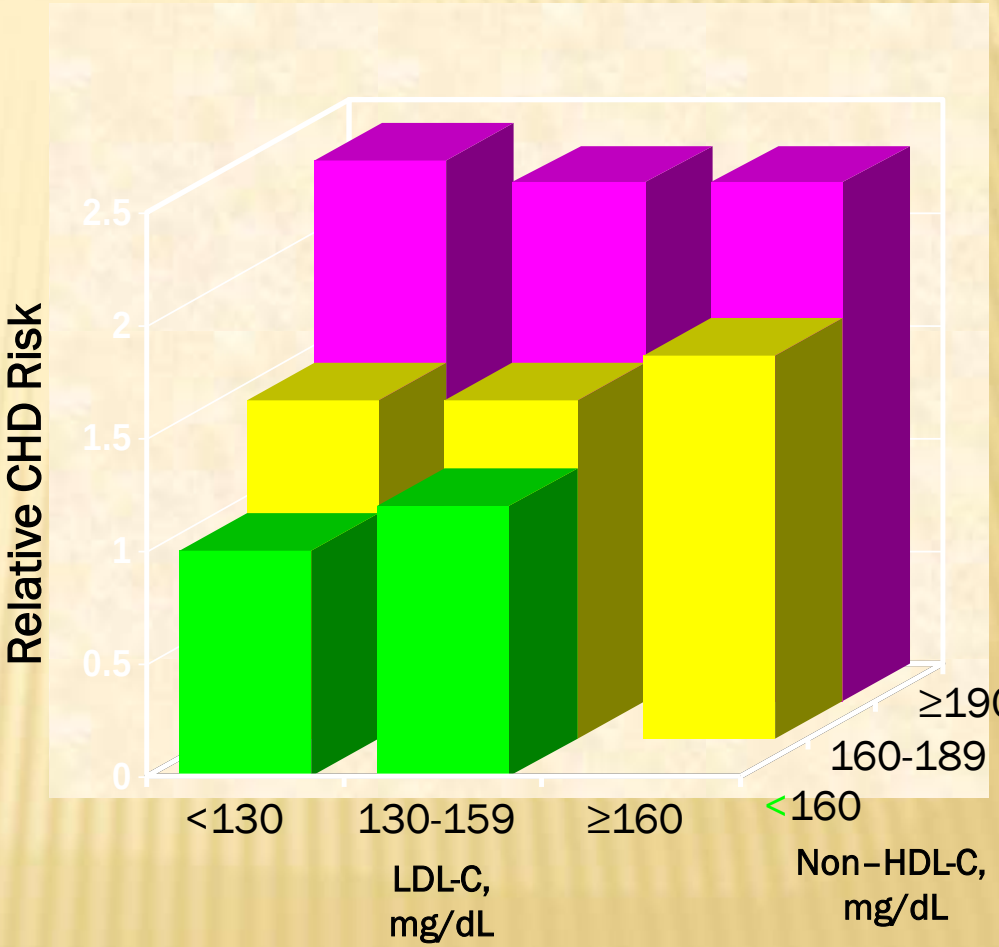
High-density lipoprotein

- Removes cholesterol from peripheral tissues

NON–HDL-C IS SUPERIOR TO LDL-C IN PREDICTING CHD RISK

The Framingham Study

- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- In contrast, a strong positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C
- Non–HDL-C is a stronger predictor of CHD risk than LDL-C



Liu J, et al. *Am J Cardiol.* 2006;98:1363-1368.

NON-HDL CHOLESTEROL (NON-HDL CHOL. ≡ TC - HDL)

Known predictor of CHD in epidemiology

Represents the sum of LDL, Lp(a), IDL, and VLDL: ----

All atherogenic apo B containing lipoproteins

Lipid Equivalent of “HbA1C”

Non–HDL-C: A Neglected CVD Risk Factor/Rx Goal

Whenever TG > 200 mg/dL

1. Non–HDL-C = Total C – HDL-C (*all* atherogenic lipids)
    1. Non–HDL-C goal = LDL-C goal + 30

Non–HDL-C Goal (mg/dL)	LDL-C Goal (mg/dL)	Patient Category
<190	<160	No CHD, 0-1 risk factors
<160	<130	No CHD, 2+ risk factors
<130	<100	CHD/CHD risk equivalent
<100	<70	CVD + DM/MS/smoker/ACS

Rx to lower Non–HDL-C

- TG >500: fibrate, omega-3, nicotinic acid, statin.
- TG 200-500: statin, ezetimibe, fibrate, omega-3, nicotinic acid, bile acid sequestrants

ACS = acute coronary syndrome MS = metabolic syndrome HTG = hypertriglyceridemia


L.D.L.

"polydisperse" to describe LDL having a wide range of particle sizes;
"monodisperse" LDL, which has a narrow range of particle size.

the LDL pattern

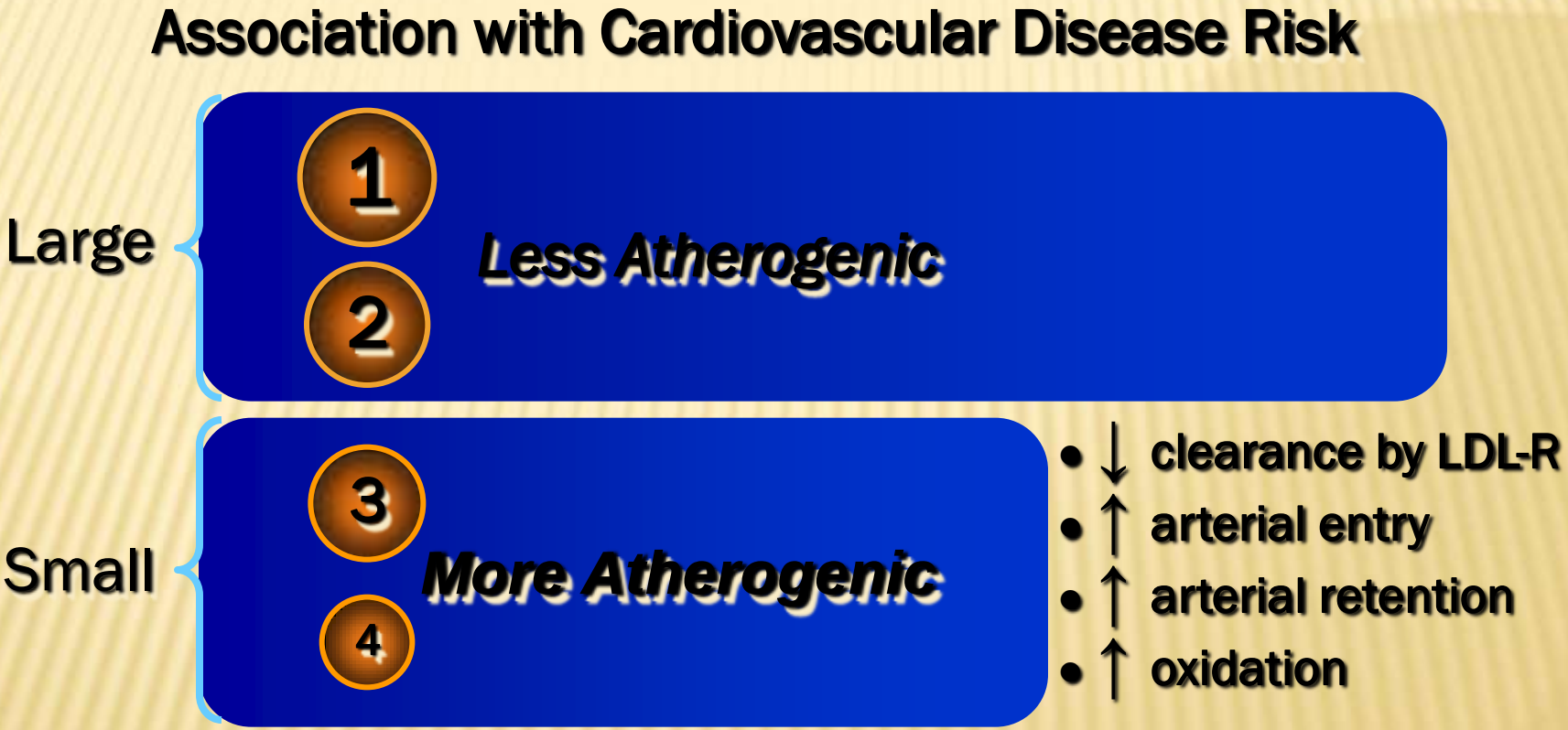
pattern A :signifies a predominance of larger particles ,typically contains "monodisperse" LDL ;

pattern B.
denotes a preponderance of smaller LDL particles
. and reflects "polydisperse" LDL;
most particles in polydisperse LDL consist of small LDL.

Pattern A is the most common and most normal LDL pattern.

the more abnormal pattern B confers increased risk for CHD . T

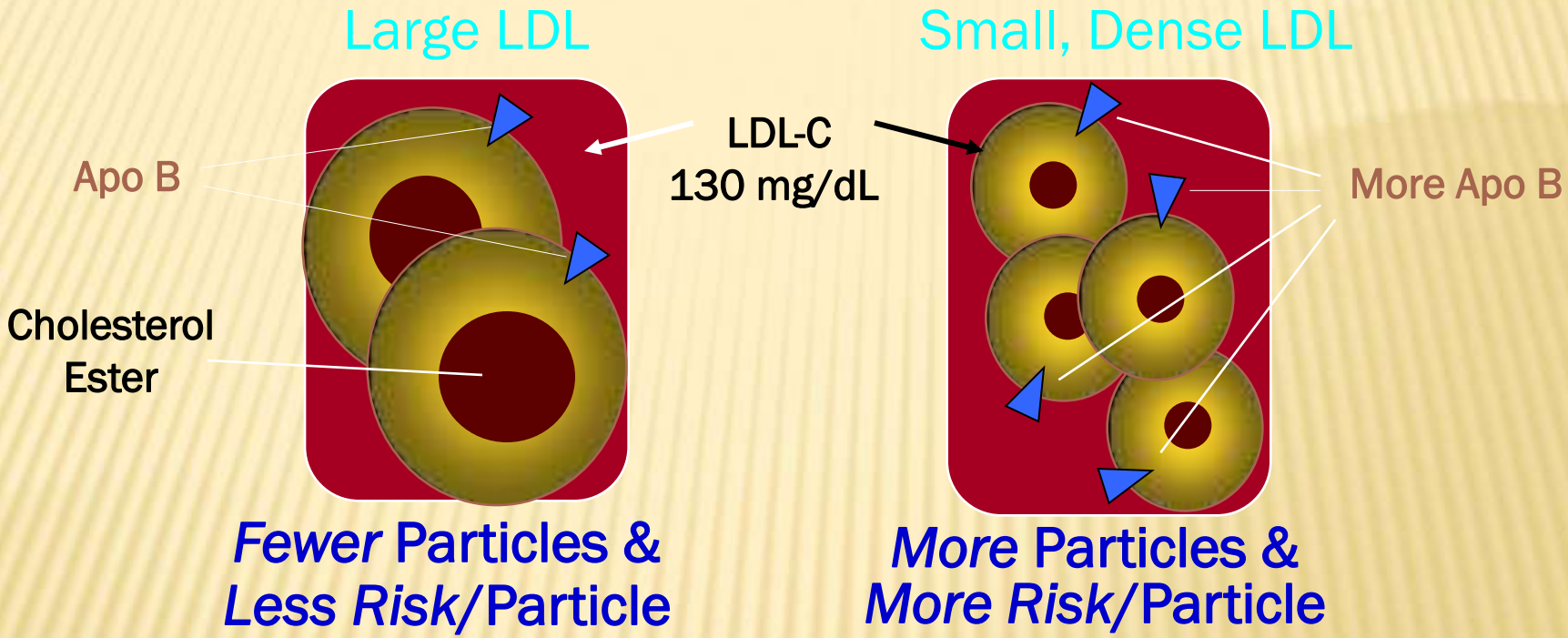
LOW-DENSITY LIPOPROTEIN (LDL) CONSISTS OF MULTIPLE DISTINCT SUBCLASSES DIFFERING IN SIZE AND LIPID CONTENT*



* Distribution of subclasses is independent of LDL-C.

Berneis KK, Krauss RM. *J Lipid Res.* 2002;43:1363-1379.

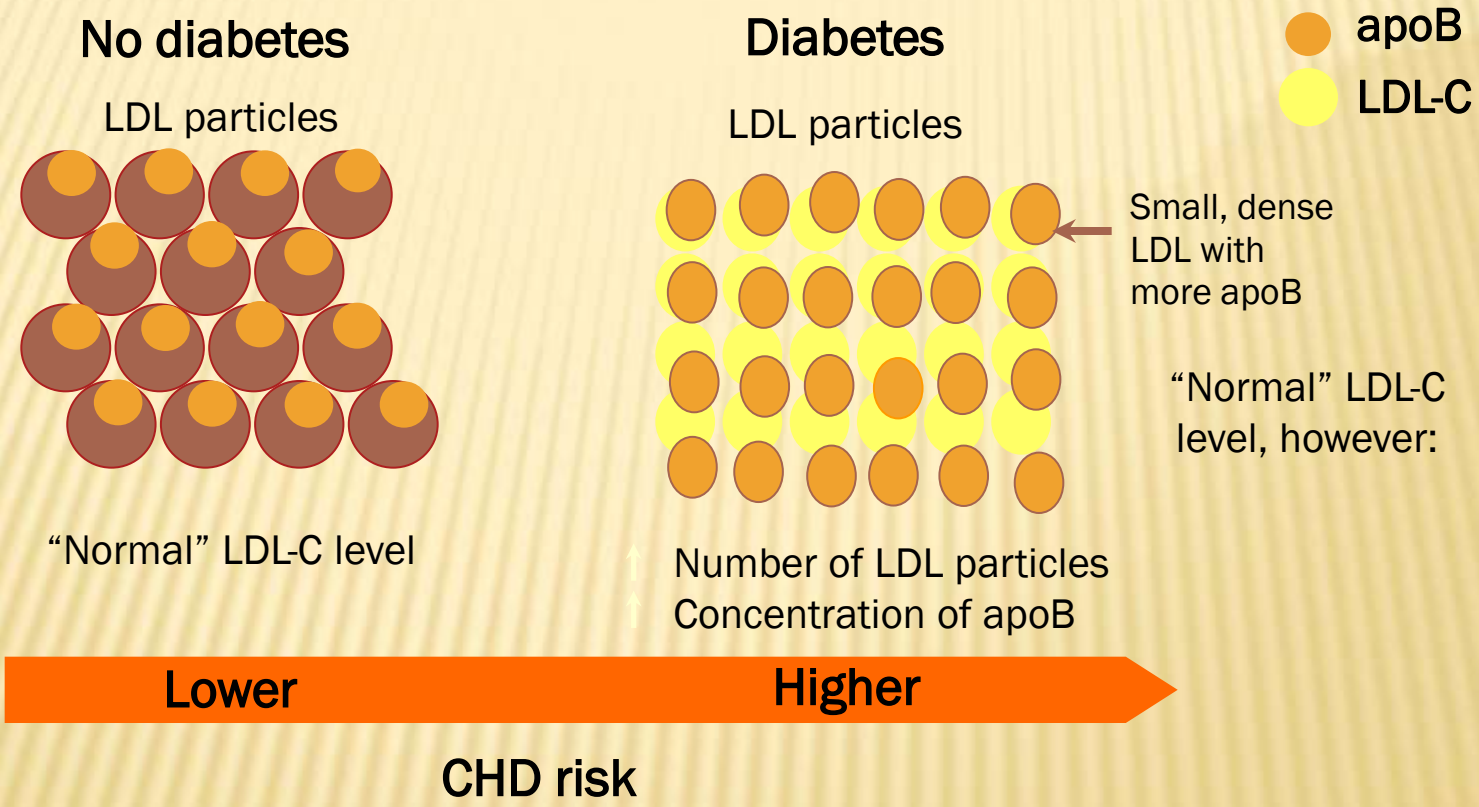
LDL-C DOUBLY *UNDER*ESTIMATES CVD RISK IN CASES OF SMALL, DENSE LDL



Otvos JD, et al. *Am J Cardiol*. 2002;90:22i-29i.

"NORMAL" LDL-C LEVELS IN PEOPLE WITH DIABETES CAN BE MISLEADING…

SMALL, DENSE LDL-C PARTICLES ARE MORE ATHEROGENIC



Adapted from Austin MA, Edwards KL *Curr Opin Lipidol* 1996;7:167-171; Austin MA et al *JAMA* 1988;260:1917-1921; Sniderman AD et al *Diabetes Care* 2002;25:579-582.

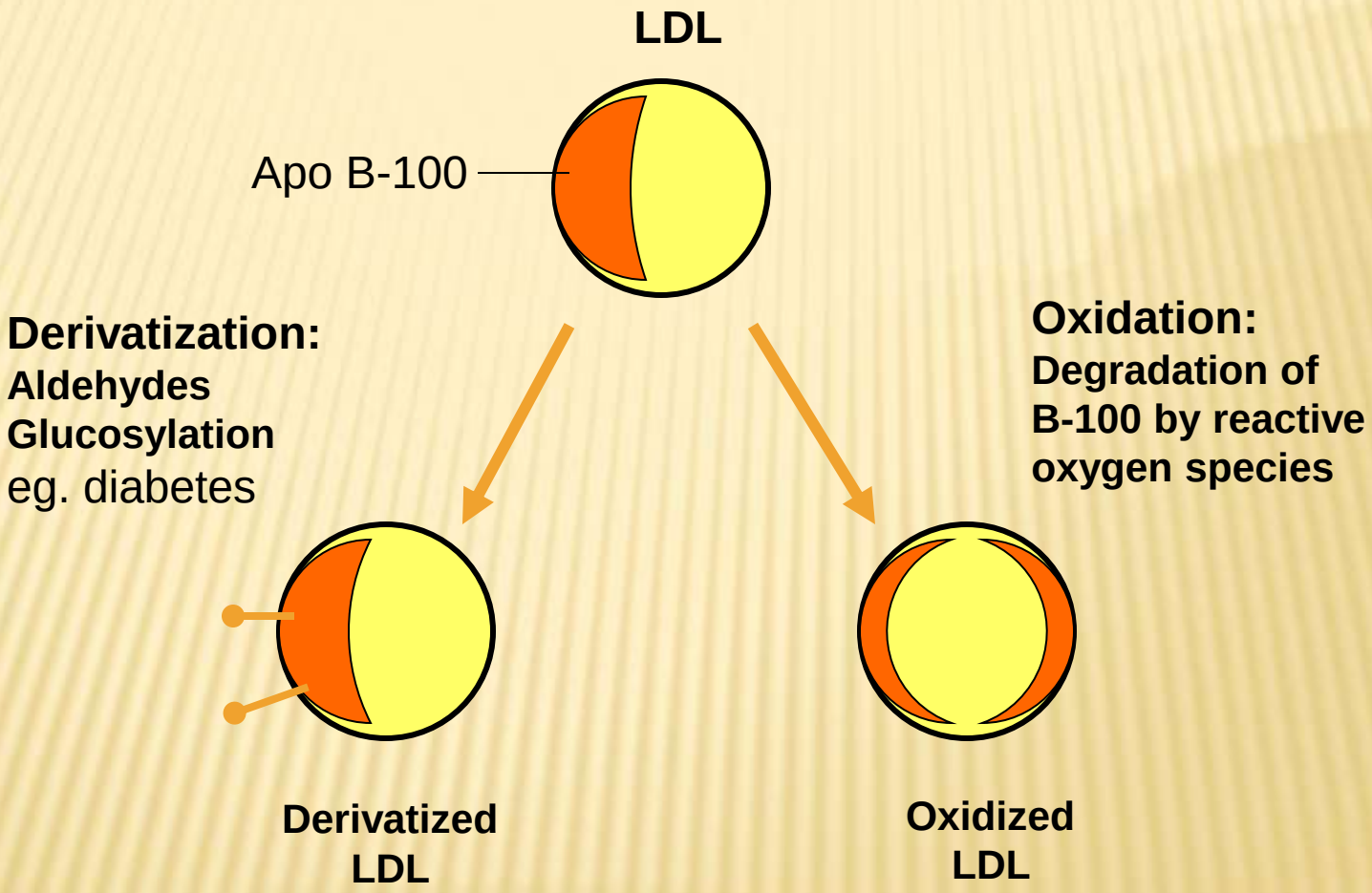
LDL-CHOLESTEROL CONCENTRATION FAILS TO PRECISELY COUNT THE NUMBER OF LDL PARTICLES.

THIS NUMBER DERIVES INSTEAD FROM THE LDL–APOLIPOPROTEIN B (APO B) LEVEL.

THERE IS ONE APO B MOLECULE PER LDL PARTICLE;

HENCE, THE LDL–APO B LEVEL ACCURATELY DEFINES LDL PARTICLE NUMBER.

MODIFICATION OF LDL



Ox-LDL :

- **Ox-LDL is more atherogenic than Native LDL.**
- **Prolonged existence in the circulation increases the likelihood of oxidation :**
  - **Small dense LDL.**
  - **As levels of LDL-C increases so does the half life of LDL particles (Days rather than hours).**
  - **Glycated Apo B impair LDL clearance.**
- **HDL contains anti-oxidant enzymes (paraoxanase), so, reduced HDL may predispose to oxidation.**

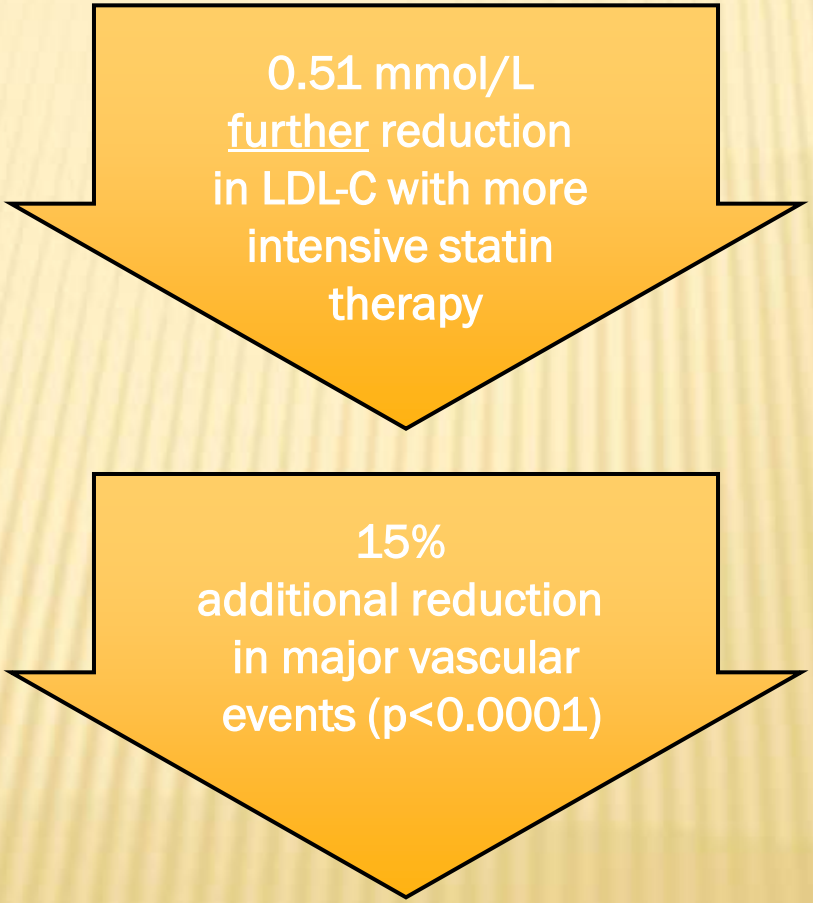
RELATIONSHIP BETWEEN CHANGES IN LDL-C AND HDL-C LEVELS AND CHD RISK

1% decrease in LDL-C reduces CHD risk by 1%[1]

1% change in HDL-C associated with 1–3% reduction in CHD risk[2–5]

J Med 1999; 341: 410-418

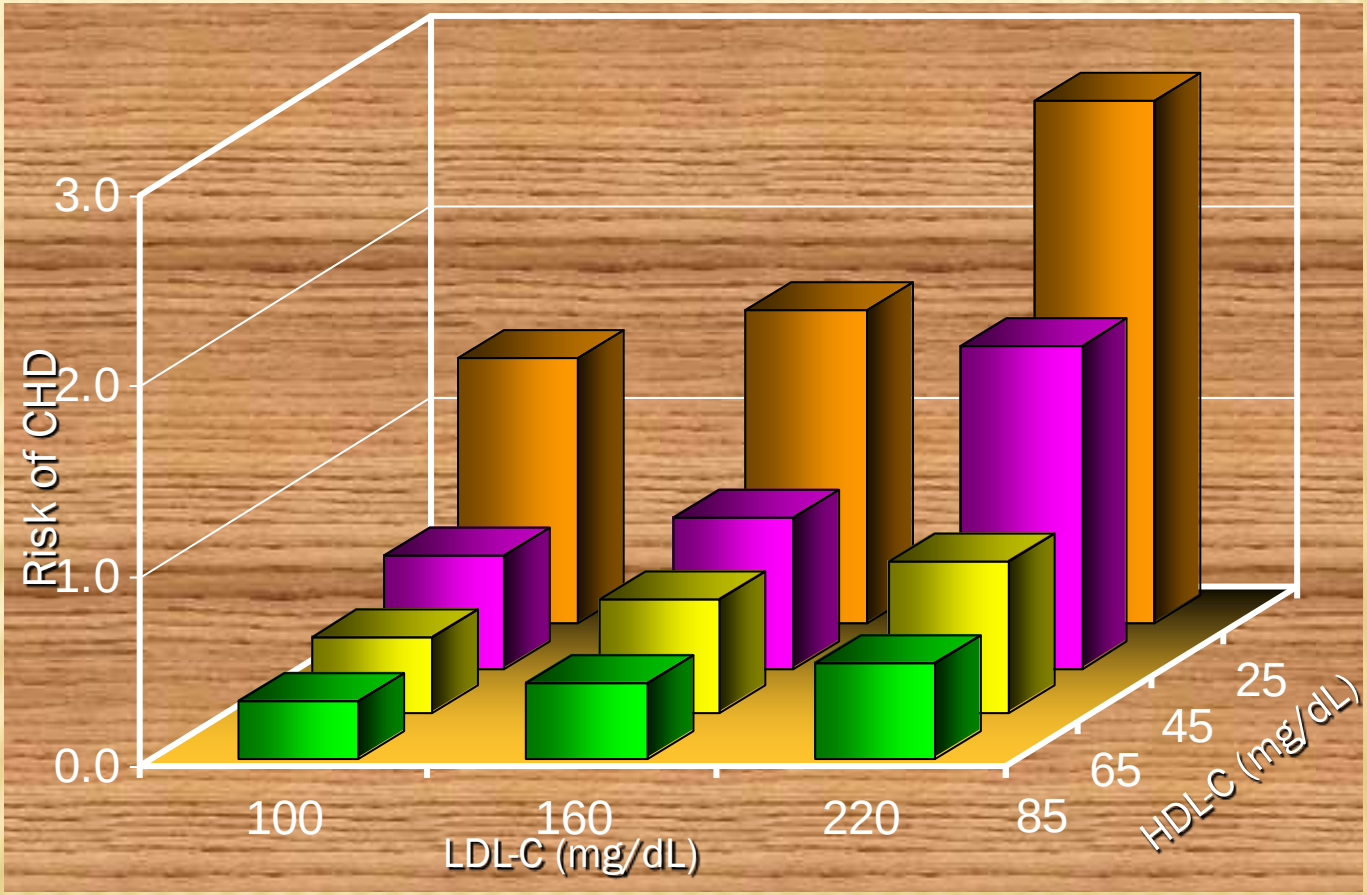
MORE VERSUS LESS INTENSIVE STATIN TREATMENT IS ASSOCIATED WITH FURTHER REDUCTIONS IN MAJOR VASCULAR EVENTS



CTT Collaborators. *Lancet* 2010; 376: 1670–1681

H.D.L.

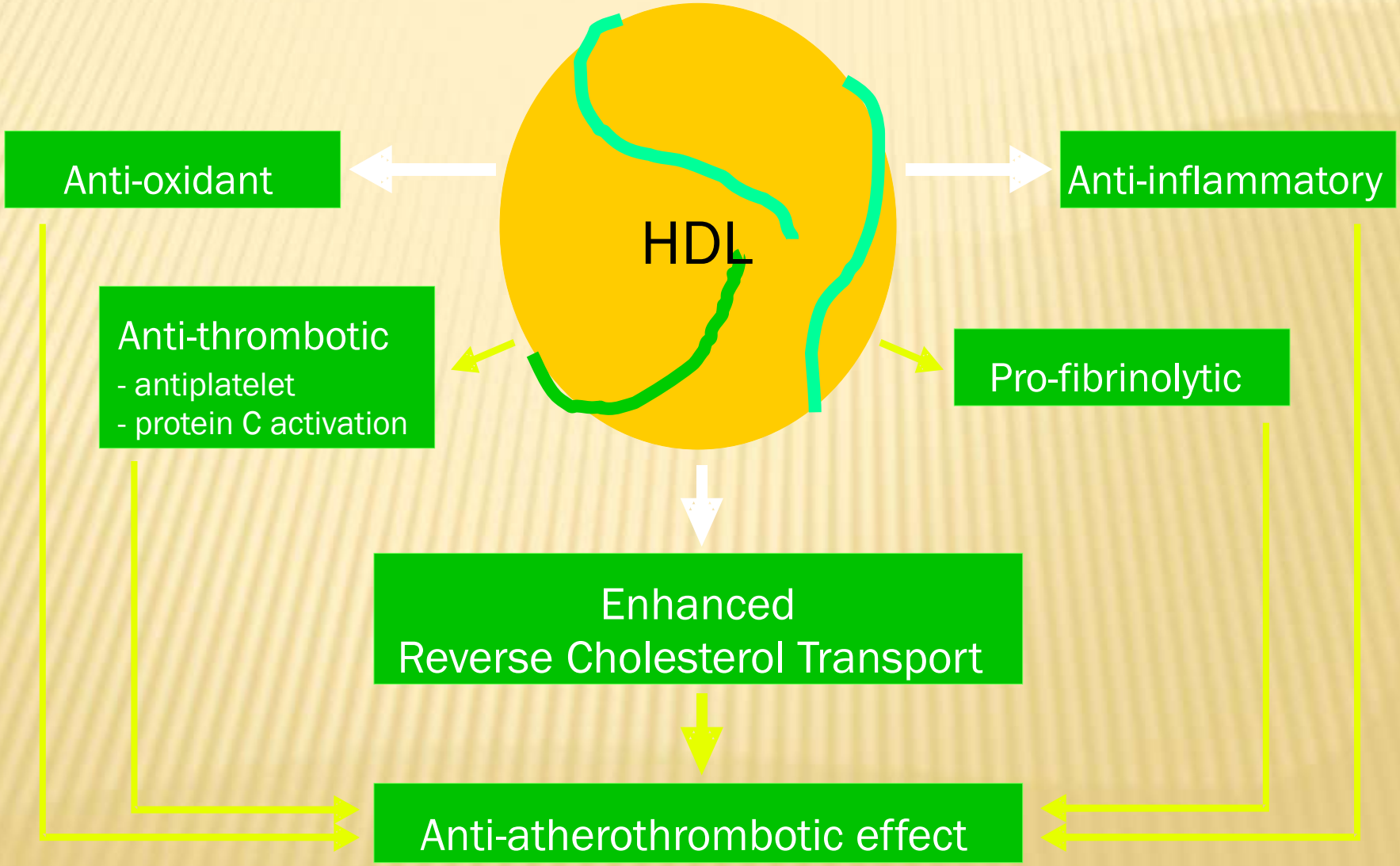
Low HDL-C: Independent Predictor of CHD Risk, Even When LDL-C is Low



Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *American Journal of Medicine*. 1977;62:707-14.

Patients with low HDL-C are 3x times more likely to die after ACS (heart attack)

Anti-atherothrombotic Actions of HDL



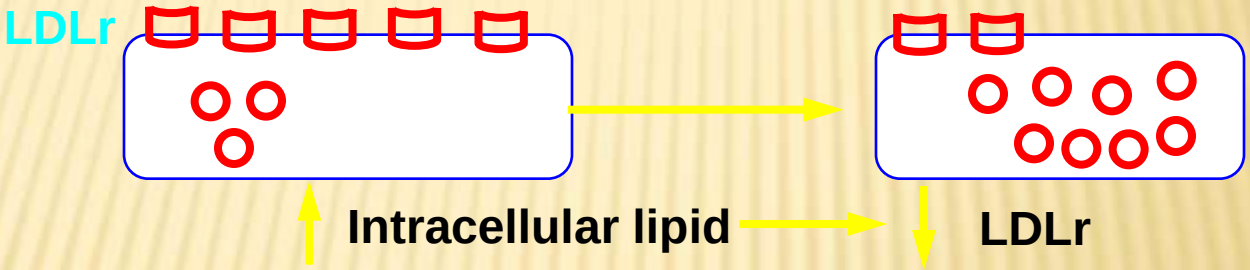
HDL density :

- The plasma triglyceride concentration is negatively correlated with that of large HDL2 and positively correlated with the level of small HDL3.
- HDL2 has the greater anti-atherogenic effect.
- HDL3 is rapidly cleared from the circulation leading to lower serum HDL-cholesterol.


Receptors

LDLr :

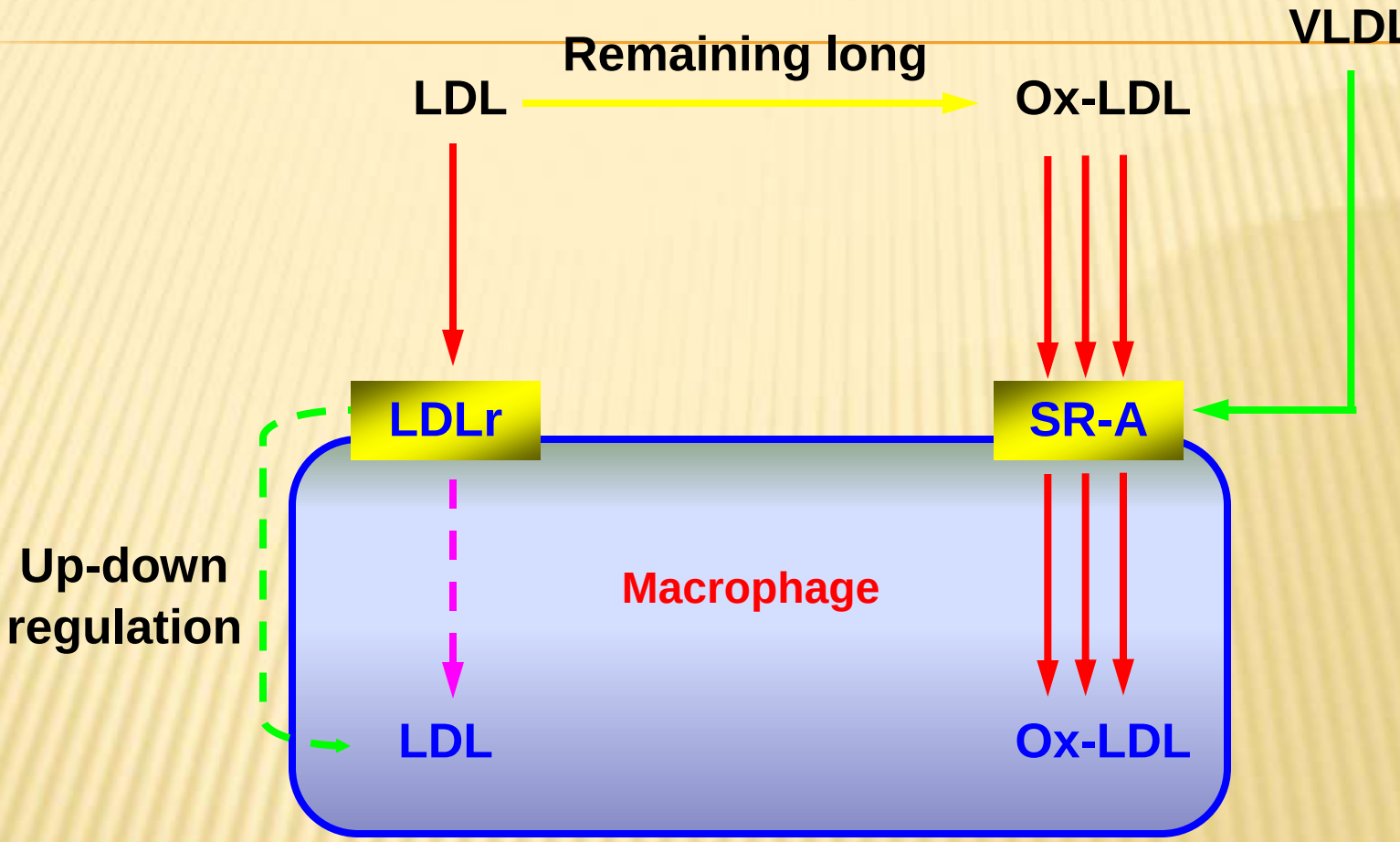
Abundant in liver and phagocytosis system. This receptor-mediated uptake of LDL is tightly regulated by the accumulation of intracellular lipid, thus preventing excessive cellular loading.



Scavenger receptor :

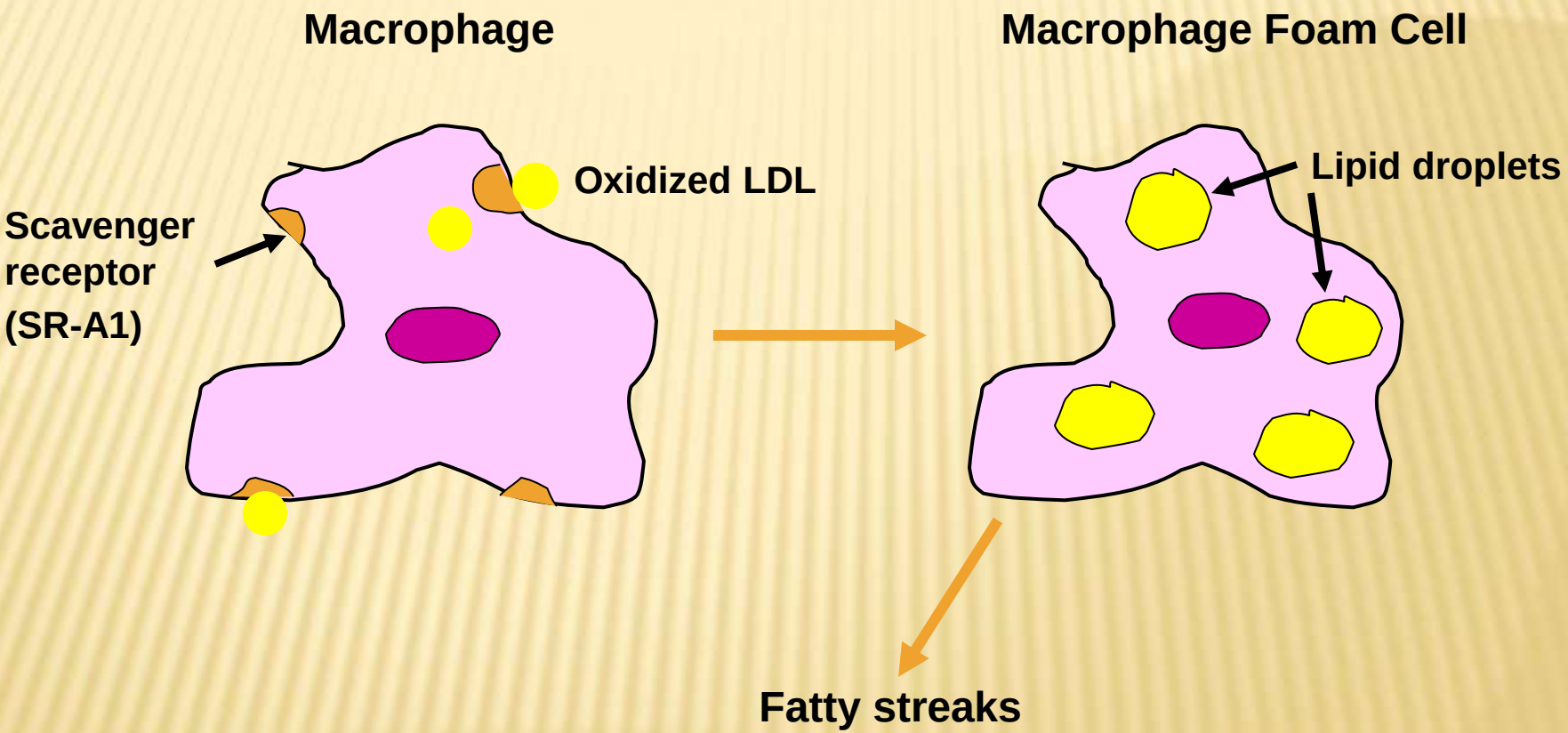
Scavenger receptors present on the phagocytes are not regulated like LDLr.

They maintain uptake of Ox-LDL and possibly VLDL until massive loading of cells with lipids “foam cells”, characteristic for atherosclerotic lesions.



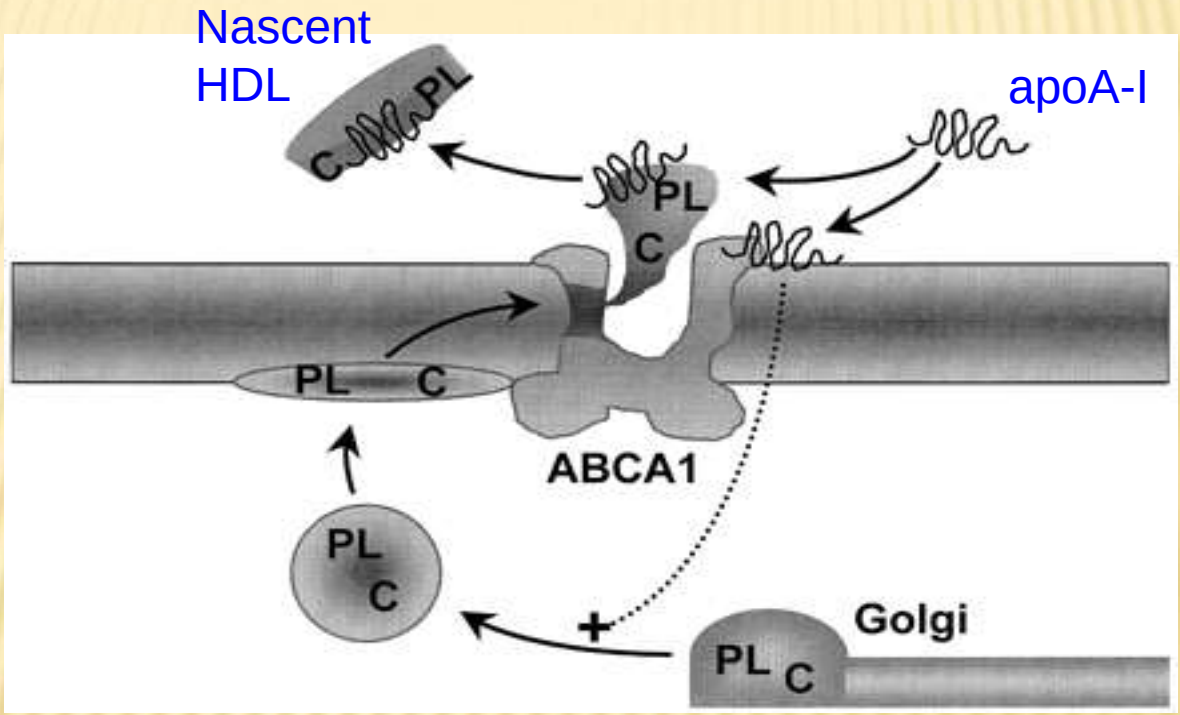
LDLr and SR-A on the surface of a macrophage

THE SCAVENGER RECEPTOR:
CLEARANCE OF MODIFIED LDL BY MACROPHAGES




Reverse cholesterol
transport

ABCA1 FUNCTION



ABCA1 Transporter/Receptor

Large plasma membrane spanning ATP dependent protein.

Essential for moving excess intracellular cholesterol and phospholipid to the plasma membrane.

Acts as a flipase, flipping cholesterol and phospholipid from inner leaflet of plasma membrane to outer leaflet.

Necessary for removing excess cholesterol from foam cells and preventing early steps in atherosclerosis.

ApoA-I is required for capturing the cholesterol released from the foam cell.

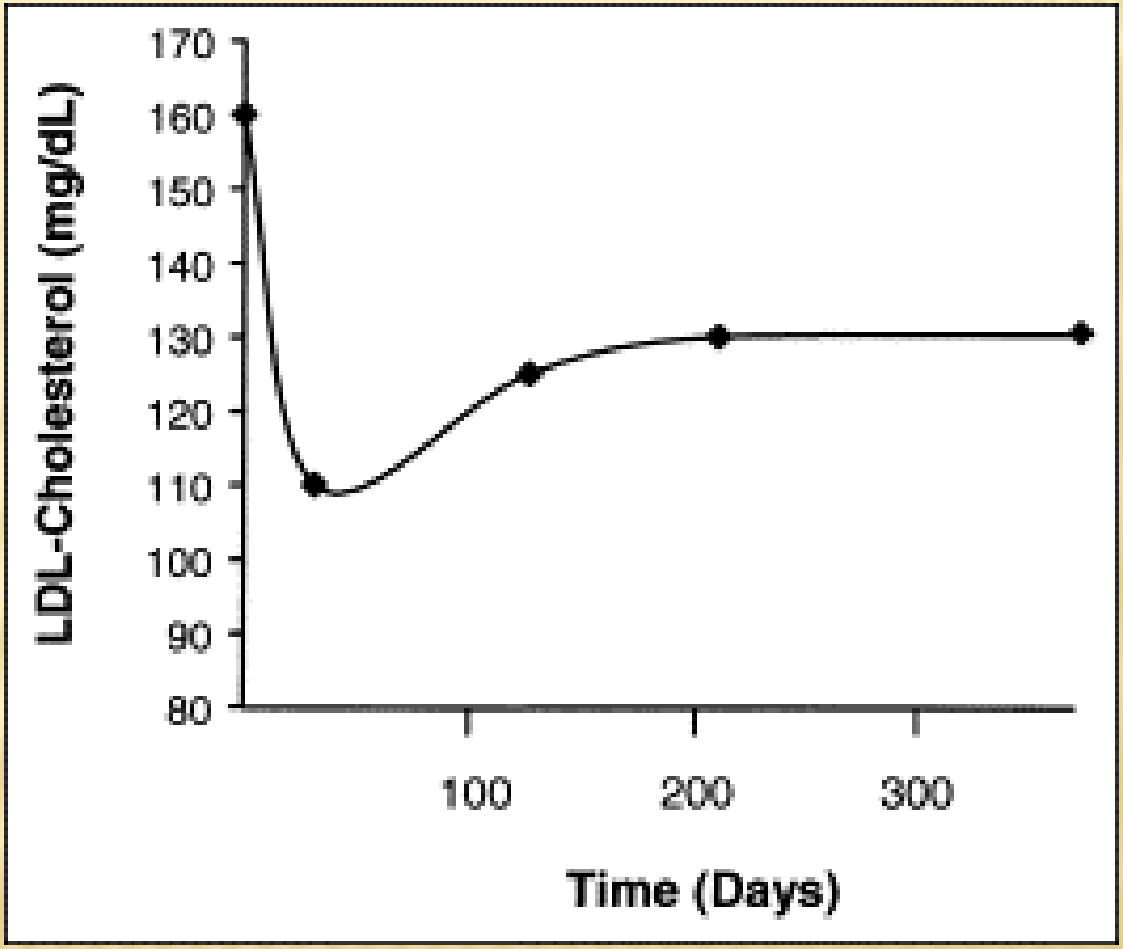
Reverse Cholesterol Transport (RCT)

The process whereby excess cholesterol in peripheral cells, especially foam cells, is returned to the liver for degradation and excretion.

RCT involves apoA-I, ABCA1 and LCAT as well as receptors on the liver for uptake of the excess cholesterol.


controversy
Tachyphylaxis?

DEVELOPMENT OF TACHYPHYLAXIS AMONG PATIENTS TAKING HMG COA REDUCTASE INHIBITORS



Adapted from William et al. The American J. of Card. 15 November 2000

- Proprotein convertase subtilisin kexin type 9 (PCSK9) is a key regulator of serum LDL-cholesterol (LDL-C) levels.

- PCSK9 is secreted by the liver into the plasma and binds the hepatic LDL receptor (LDLR), causing its subsequent degradation.

- It is demonstrated that a moderate dose of atorvastatin (40 mg) increases PCSK9 serum levels, suggesting why increasing statin doses may have diminished efficacy with regard to further LDL-C lowering

- suggest an explanation for why increasing doses of statins fail to achieve proportional LDL-C lowering.


hyper- triglyceridemic waist.?

- *the simultaneous presence of fasting hypertriglyceridemia and of an enlarged waistline would be predictive of excess visceral adiposity, a clinical phenotype that was first described as "hyper-triglyceridemic waist."*

- *The size of the epicardial or pericardial fat depot is significantly associated with the cardiometabolic risk profile.*

- *Increased epicardial fat may also contribute to an increased local release of cytokines/adipokines that may impair the vasodilatory response of coronary vessels under certain physiological stress conditions.*

CHECKING LIPIDS

- Nonfasting lipid panel
  - measures HDL and total cholesterol
- Fasting lipid panel
  - Measures HDL, total cholesterol and triglycerides
  - LDL cholesterol is calculated:
    - LDL cholesterol = total cholesterol – (HDL + triglycerides/5)

WHOM TO SCREEN FOR DYSLIPIDEMIA?

By age alone: ×

Men over age 40 +

Women over age 50 (or post-menopausal) +

Other risk factors (at any age): ×

DM, HTN, Smoking, Abdominal Obesity +

Family history of early cardiovascular disease +

Physical signs of hyperlipidemia (at any age): ×

Xanthomata, xanthelasmas, arcus corneae, etc +

Evidence of existing atherosclerosis (at any age) ×

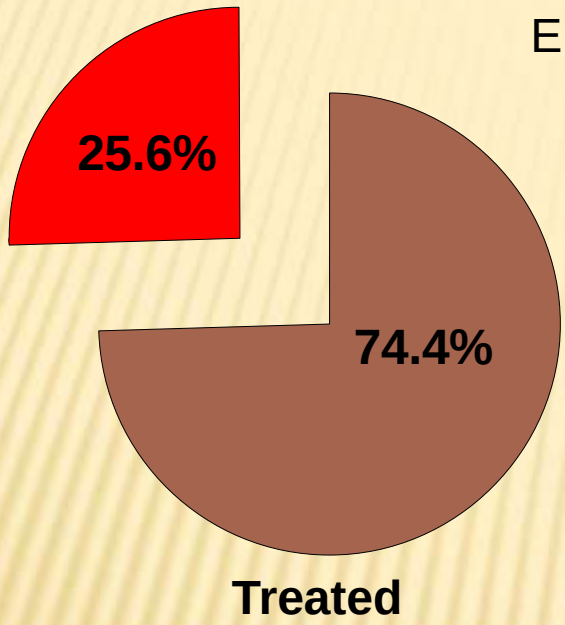

N.B.

DYSLIPIDAEMIA REMAINS UNDER-TREATED

DYSLIPIDAEMIA REMAINS UNDERTREATED AND MANY PATIENTS DO NOT REACH TREATMENT GOAL

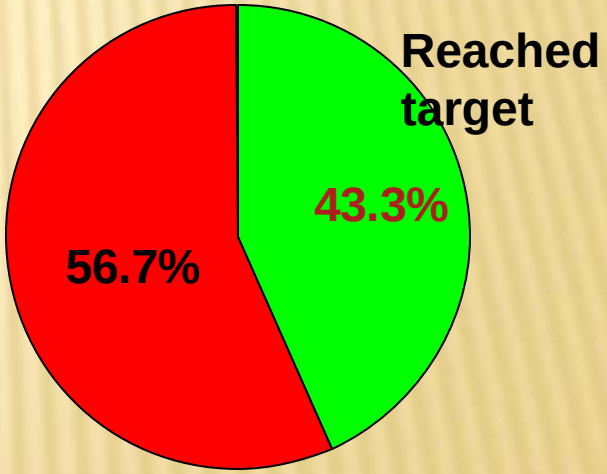
THE EURIKA STUDY

- Of 4407 patients with dyslipidaemia included in the EURIKA study, 74% received lipid-lowering agents



Treated patients

who reached target

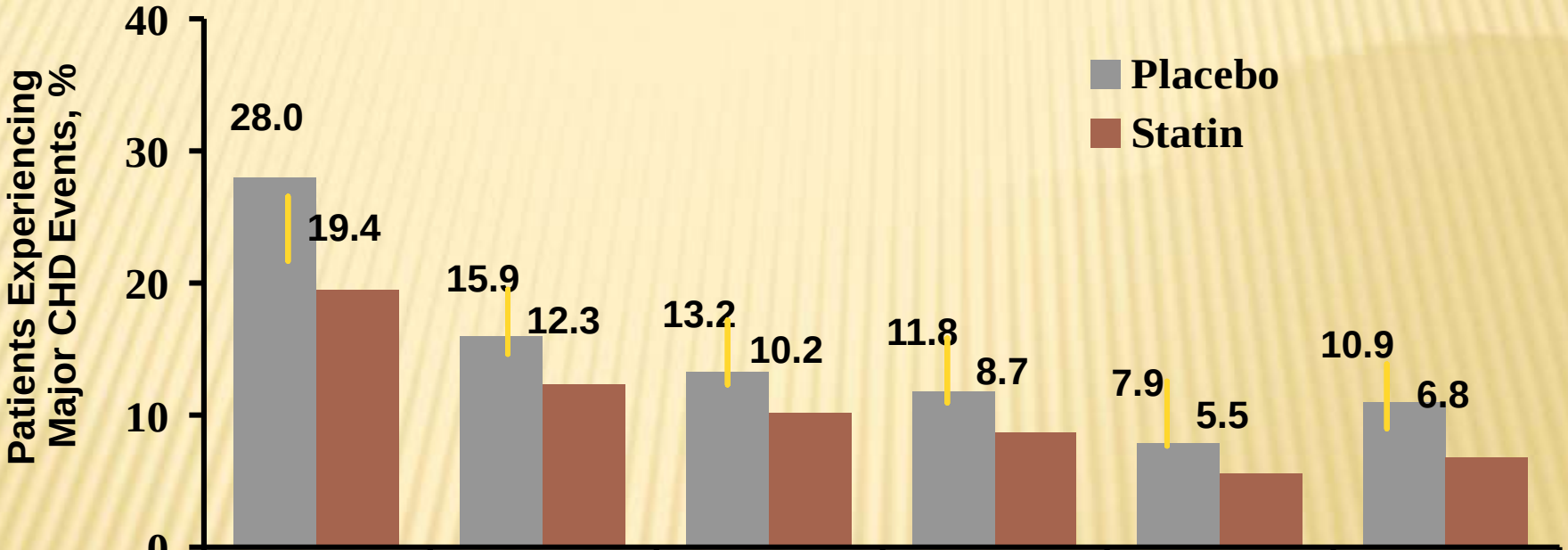


- Only 43% of treated patients reached total cholesterol goal of <5 mmol/L

Banegas J et al. *Eur J Heart* 2011;

Residual Cardiovascular Risk in Major Statin Trials

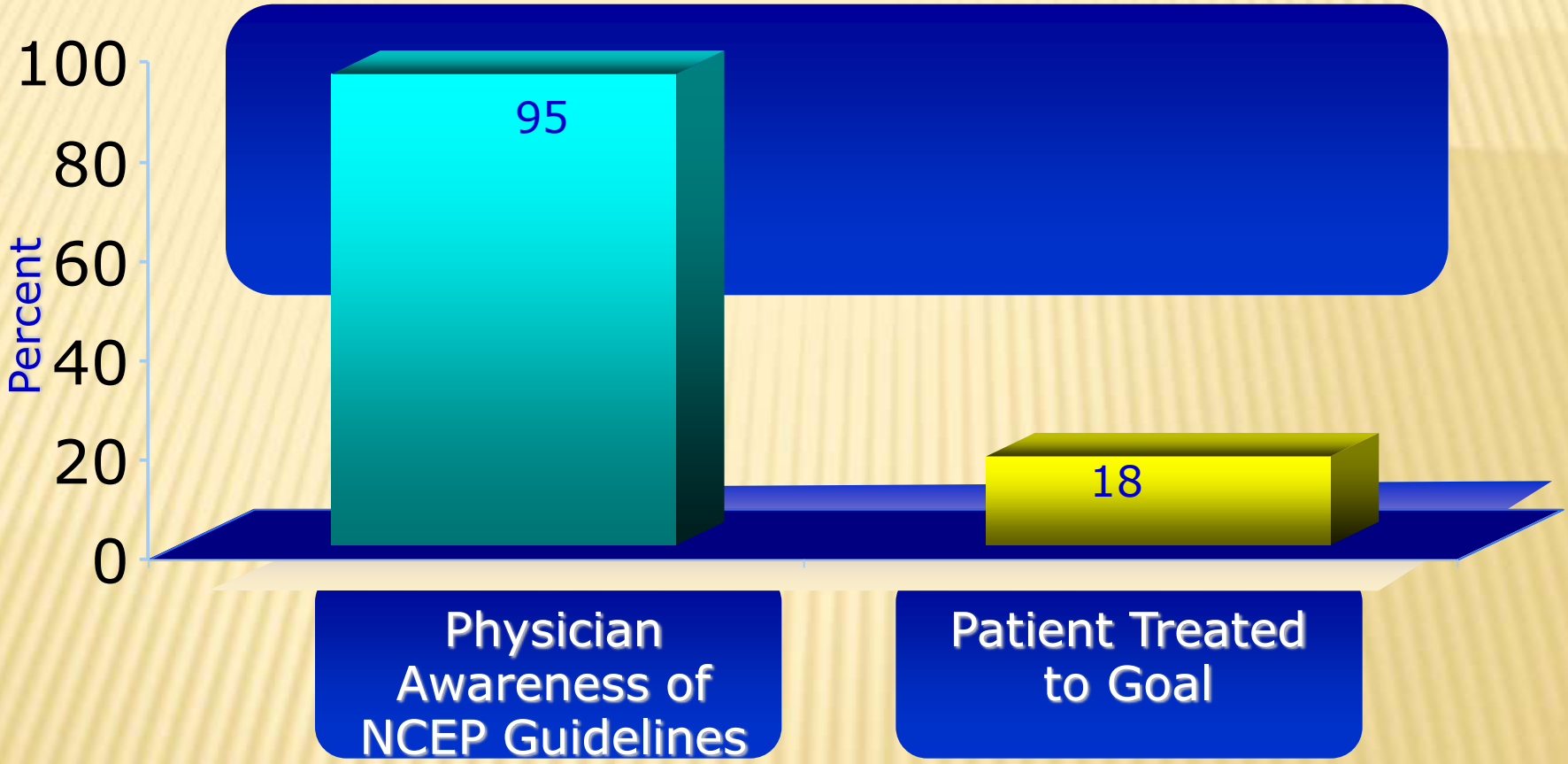
CHD events occur in patients treated with statins



	4S[1]	LIPID[2]	CARE[3]	HPS[4]	WOSCOPS[5]	AFCAPS/ TexCAPS[6]
N	4444	9014	4159	20 536	6595	6605
Δ LDL-C	-35%	-25%	-28%	-29%	-26%	-25%
	Secondary			High Risk	Primary	

[1] 4S Group. *Lancet.* 1994;344:1383-1389.
[2] LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357.
[3] Sacks FM, et al. *N Engl J Med.* 1996;335:1001-1009.
[4] HPS Collaborative Group. *Lancet*. 2002;360:7-22.
[5] Shepherd J, et al. *N Engl J Med.* 1995;333:1301-1307
[6] Downs JR, et al. *JAMA.* 1998;279:1615-1622.

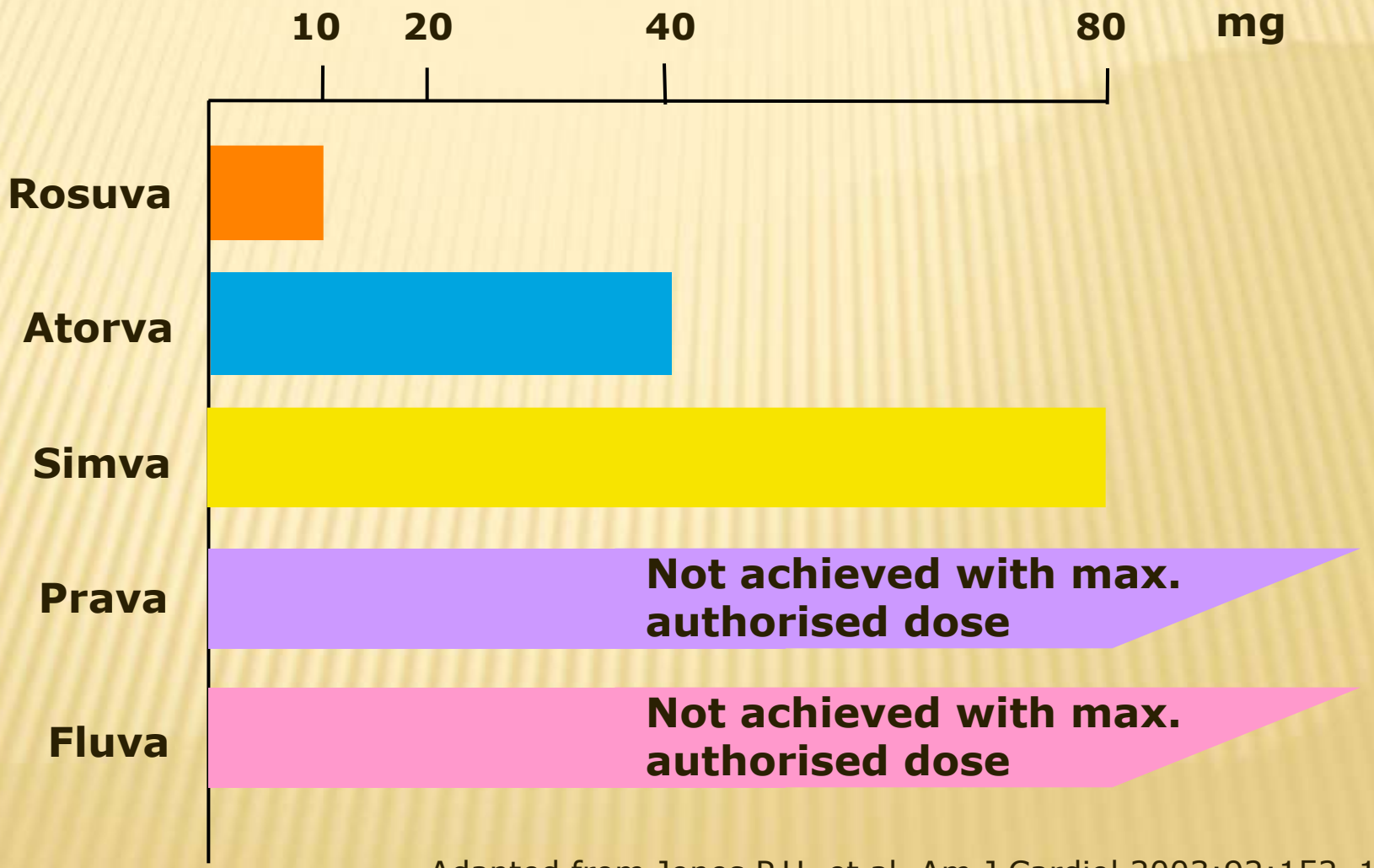
CHD Patient Treatment Gap: L-TAP



Provider awareness does not equal successful implementation

Pearson TA et al. *Arch Intern Med* 2000;160:459-467.

Statin Dose Required to Achieve 45–50% LDL-C Reduction



Adapted from Jones P.H. et al. Am J Cardiol 2003;92:152–160


Follow-Up

FOLLOW-UP

Lipids: ✖

6 weeks after start / change of dose (levels reach steady state within 6 weeks of start/change of medication) +

Long-term follow-up every 6-12 months +

AST / ALT / CK: ✖

Get baseline +

Repeat whenever you test lipids: +

6 weeks after a dose increase ×

Every 6-12 months ×

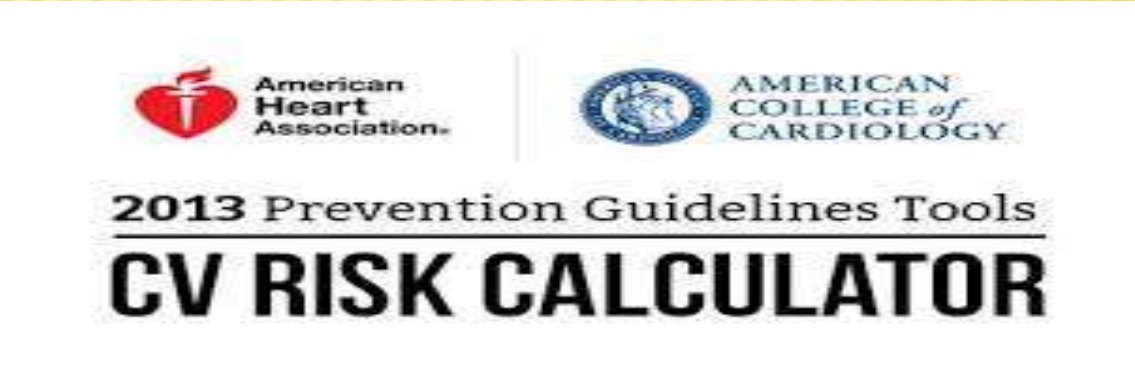
Check more frequently: +

If on maximum doses ×

If on combination therapy (especially a statin plus a fibrate) ×

Check if symptomatic +

OVERVIEW OF THE 2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS



HISTORY OF U.S. DYSLIPIDEMIA GUIDELINE DEVELOPMENT

ATP I[1]	ATP II[2]	ATP III[3]	ATP III Update[4]	ACC/AHA Guidelines[5]
• Exclusive focus on LDL-C	• Risk assessment guides therapy	• Lower LDL-C threshold for therapy initiation in high risk patients	• Lower LDL-C threshold for therapy initiation in very high risk patients	• Use of moderate- or high-intensity statin therapy for patients across 4 major groups at risk for ASCVD*

*ASCVD, Atherosclerotic Cardiovascular Disease

1. NCEP. *Arch Intern Med* .1988;148:36-69. 2. NCEP ATP II. *Circulation* .1994;89:1333-445. 3. NCEP ATP III. *Circulation*. 2002;106:3143.
4. Grundy SM, et al. *Circulation*. 2004;110:227-239.. 5. Stone NJ, et al. *J Am Coll Cardiol.* 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

WHAT REMAINS THE SAME

- Ultimate goals: prevent ASCVD and improve the management of patients with ASCVD
- Heart-healthy lifestyle habits are the foundation for ASCVD prevention
- LDL-C is key treatment target
- Evidence supports that lowering LDL-C with statins reduces CV morbidity and mortality
- Benefit / Risk assessments are necessary

Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report . *Circulation*. 2002;106:3143.

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

2013 ACC/AHA CHOLESTEROL TREATMENT GUIDELINE RECOMMENDATIONS

FOCUS ON ASCVD RISK REDUCTION: 4 STATIN BENEFIT GROUPS*

Clinical ASCVD†	LDL-C level ≥190 mg/dL
Diabetes, aged 40-75 years, with LDL-C 70-189 mg/dL	Estimated 10-year risk of ASCVD of ≥7.5%,‡ 40-75 years of age, and with LDL-C 70-189 mg/dL

* Moderate- or high-intensity statin therapy recommended for these 4 groups

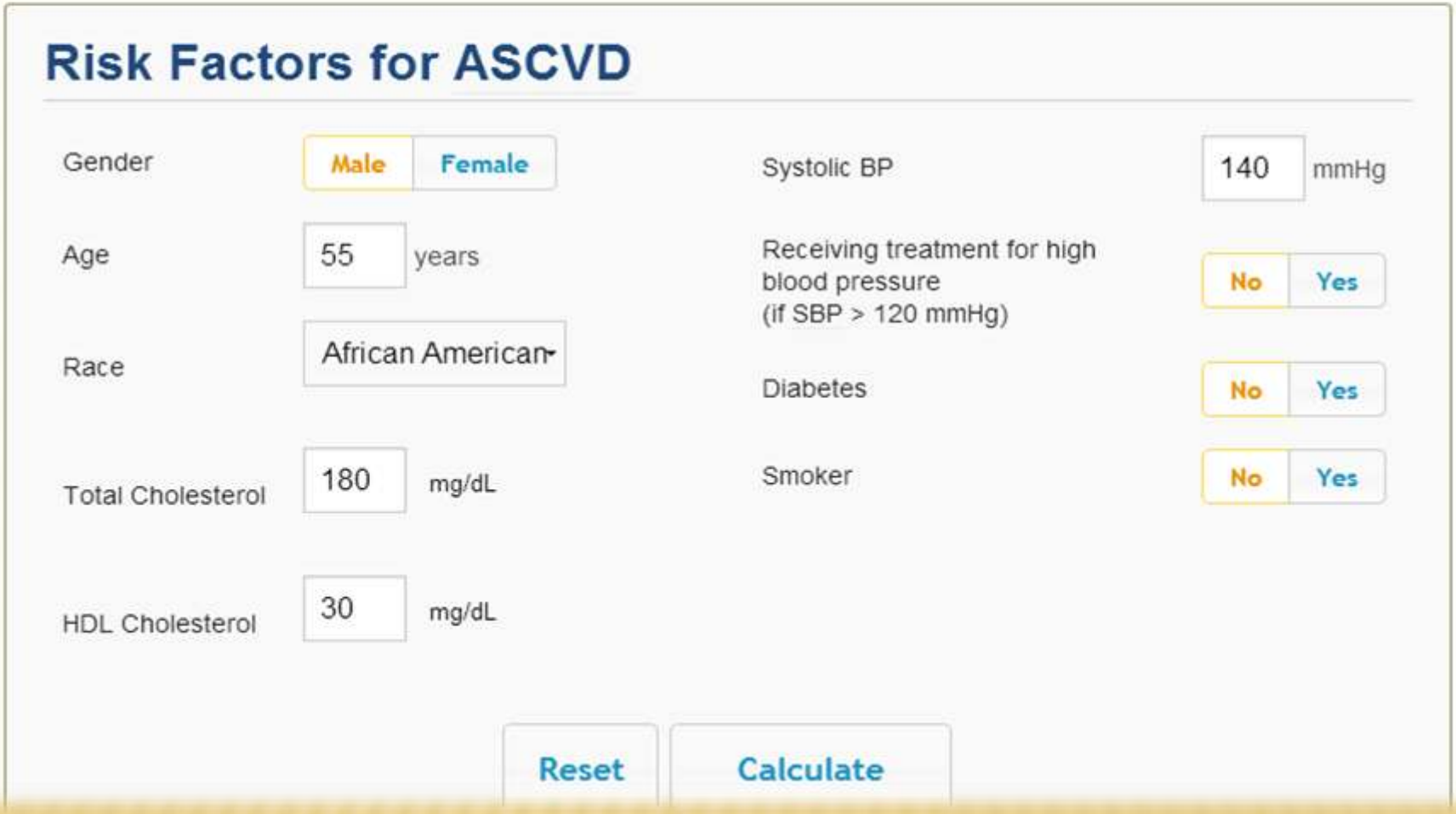
† Clinical ASCVD defined as acute coronary syndromes, history of MI, stable or unstable angina, coronary or arterial revascularization, stroke, transient ischemic attacks, or peripheral artery disease

‡ Estimated using Pooled Cohort Risk Assessment Equations

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

Pooled Cohort Risk Assessment Equations

- Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event



INTENSITY OF STATIN THERAPY

High-Intensity Statin Therapy	Moderate-Intensity Stain Therapy	Low-Intensity Statin Therapy
LDL–C ↓ ≥50%	LDL–C ↓ 30% to <50%	LDL–C ↓ <30%
Atorvastatin (40†)–80 mg Rosuvastatin 20 *(40)* mg	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

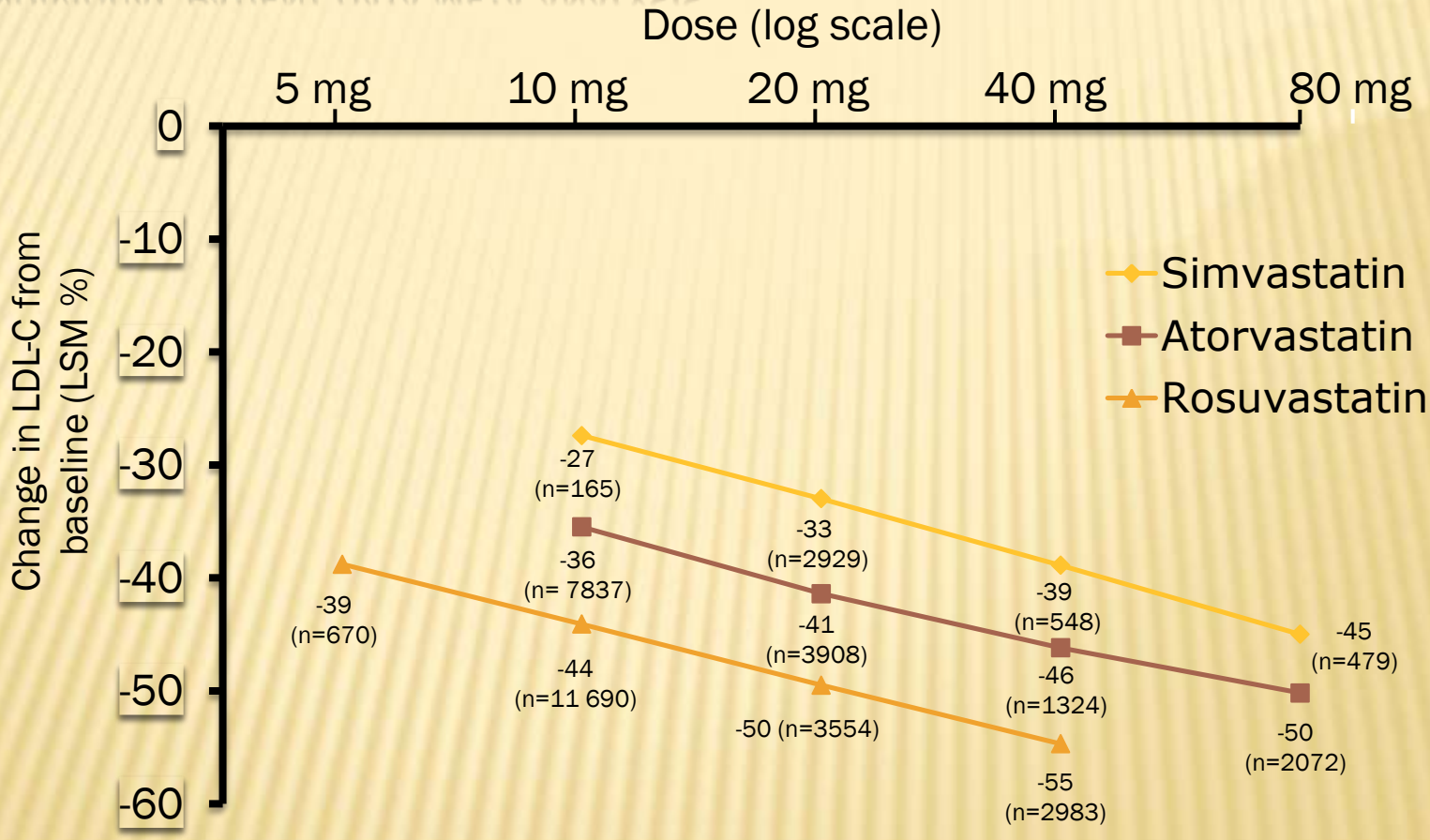
Lifestyle modification remains a critical component of ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies.

Statins/doses that were not tested in randomized controlled trials (RCTs) reviewed are listed in *italics*
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL
‡Initiation of or titration to simvastatin 80 mg not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

CHANGE IN LDL-C LEVELS WITH INCREASING DOSE OF EACH STATIN

RESULTS FROM THE WHOLE POPULATION VOYAGER INDIVIDUAL PATIENT DATA META-ANALYSIS



Rosuvastatin 10–40 mg significantly superior to equal and double doses of atorvastatin and simvastatin ($p<0.001$)

Nicholls SJ et al. *Am J Cardiol* 2010; 105: 69–76

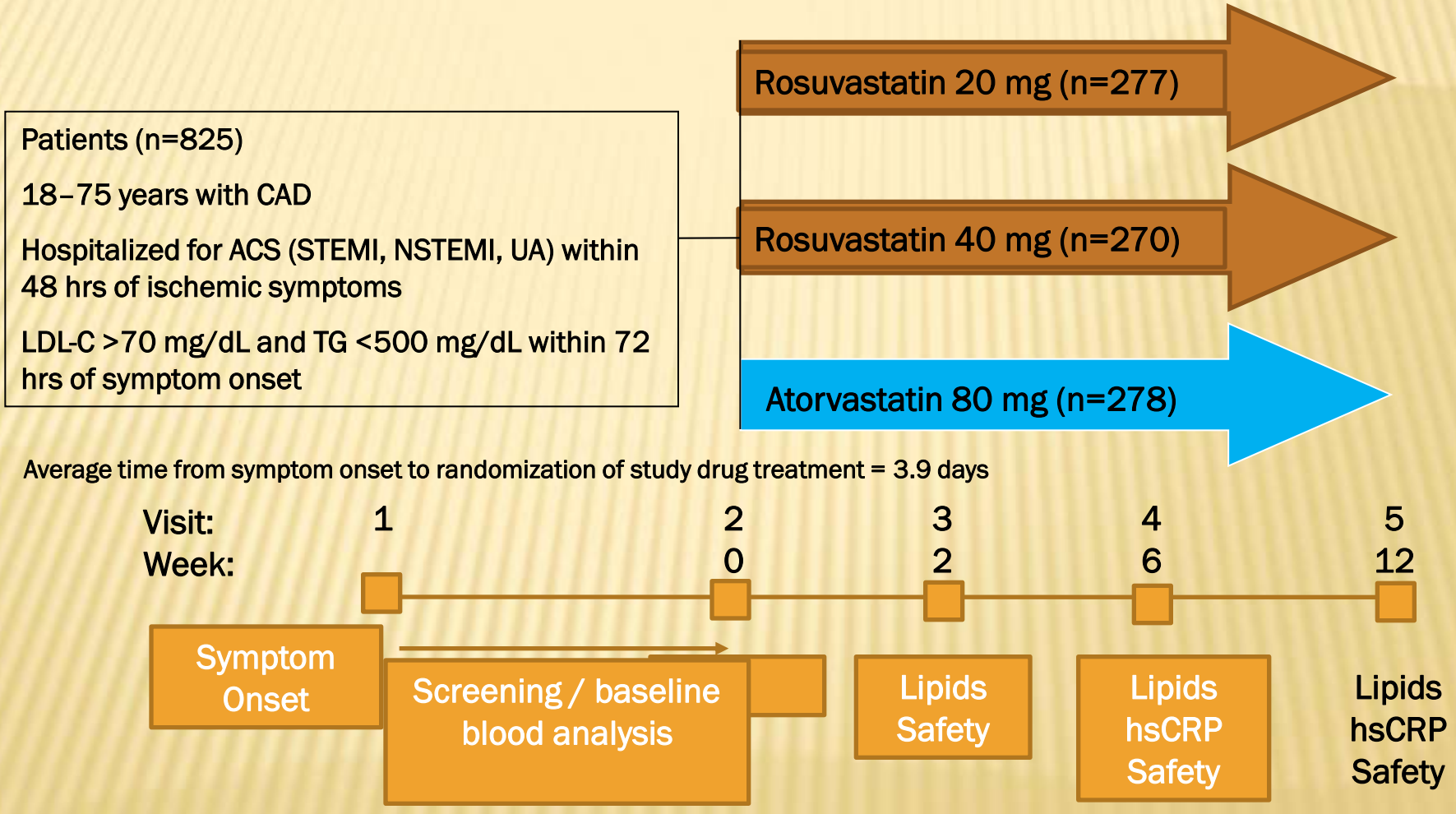
SECONDARY PREVENTION

- *Moderate-intensity* statin therapy is recommended for patients with clinical ASCVD age >75 years, or in those patients who are not candidates for high-intensity statin therapy due to safety or tolerability considerations.

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

LUNAR

Efficacy on atherogenic Lipids in ACS Patients

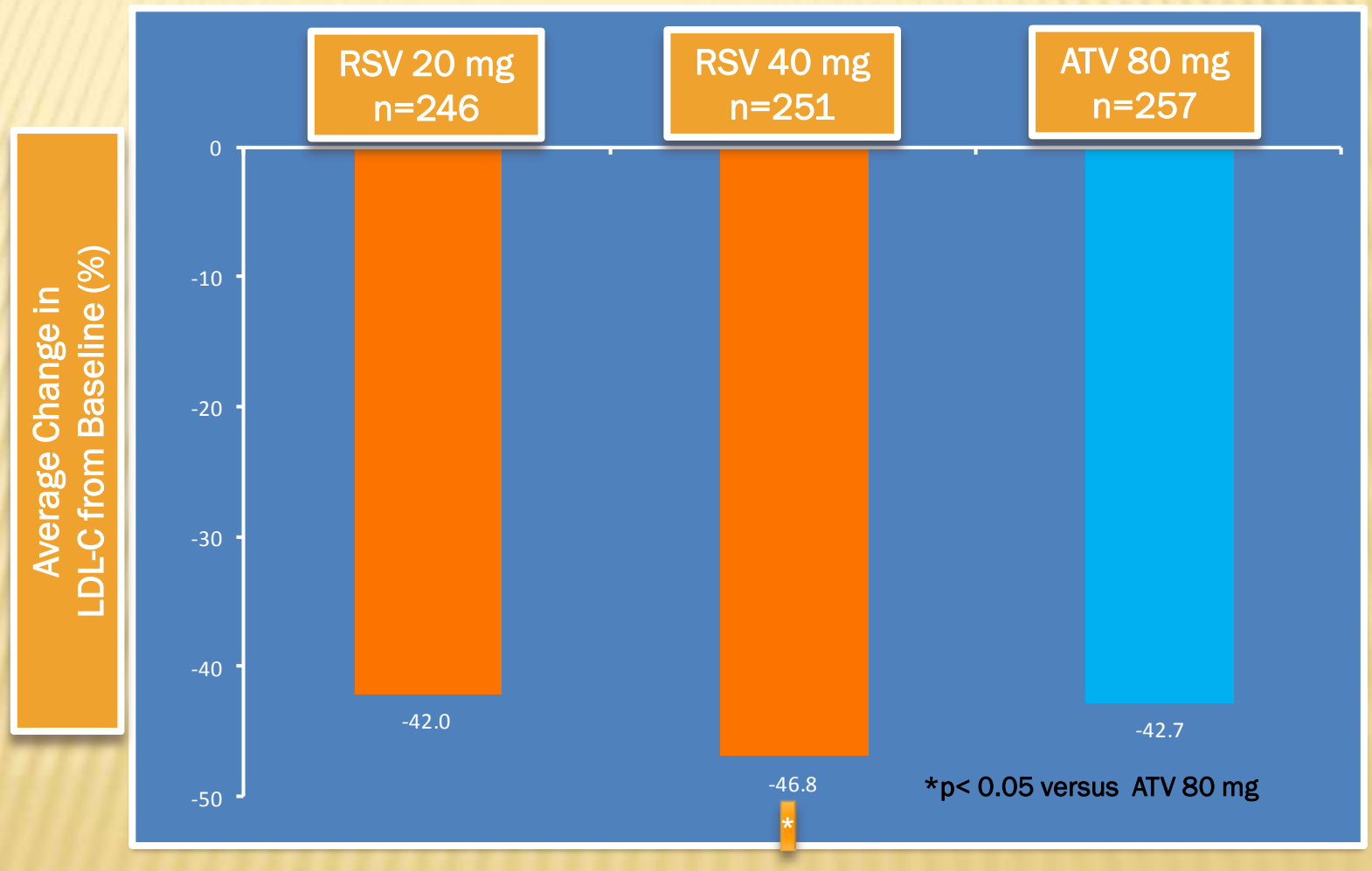


Pitt B et al. *Am J Cardiol.* 2012;109:1239-1246.

LUNAR

Primary End Point

LDL-C Averaged Over Measurements at Weeks 6 and 12



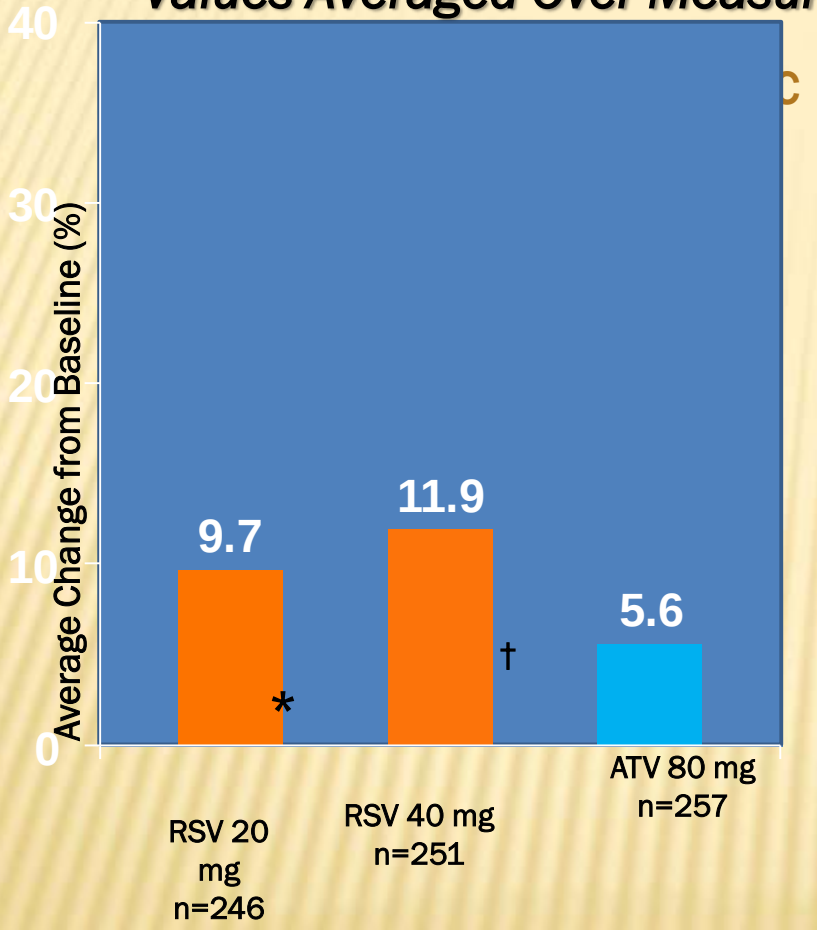
Similar results were achieved in all subcategories of ACS (unstable angina, non-STEMI, and STEMI)

Pitt B et al. *Am J Cardiol.* 2012;109:1239-1246.

LUNAR

Secondary End Point

Values Averaged Over Measurements at Weeks 6 and 12



Pitt B et al. *Am J Cardiol.* 2012;109:1239-1246.

Our findings indicate that patients recently hospitalized for an acute coronary syndrome benefit from early and continued lowering of LDL-C to levels substantially below current target levels.

CRESTOR™

Cannon CP, Braunwald E, McCabe CH, et al. *N Engl J Med* 2004;350:15 www.nejm.org

PRIMARY PREVENTION

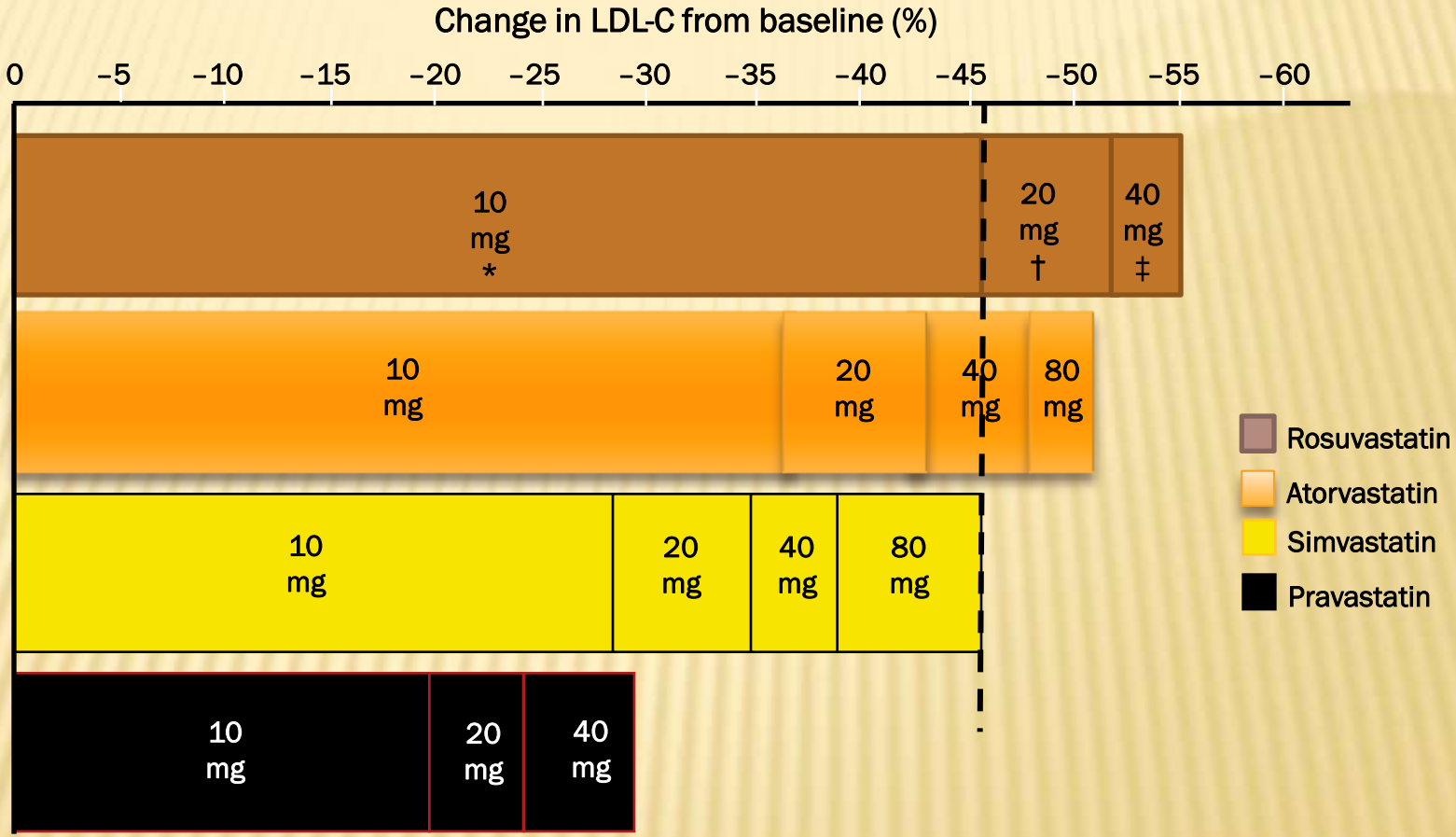
Patients ≥21 years old with LDL-C ≥190 mg/dL → **High-Intensity Statin**

- If high-intensity statin not tolerated, use maximum tolerated statin intensity
- After maximum statin intensity has been achieved, addition of a non-statin drug to further lower LDL-C may be considered

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

ROSUVASTATIN VERSUS COMPARATORS: LDL-C EFFICACY AT 10MG DOSE

THE STELLAR STUDY



*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
†p<0.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg
‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

Adapted from Jones P et al. *Am J Cardiol* 2003; 92: 152–160

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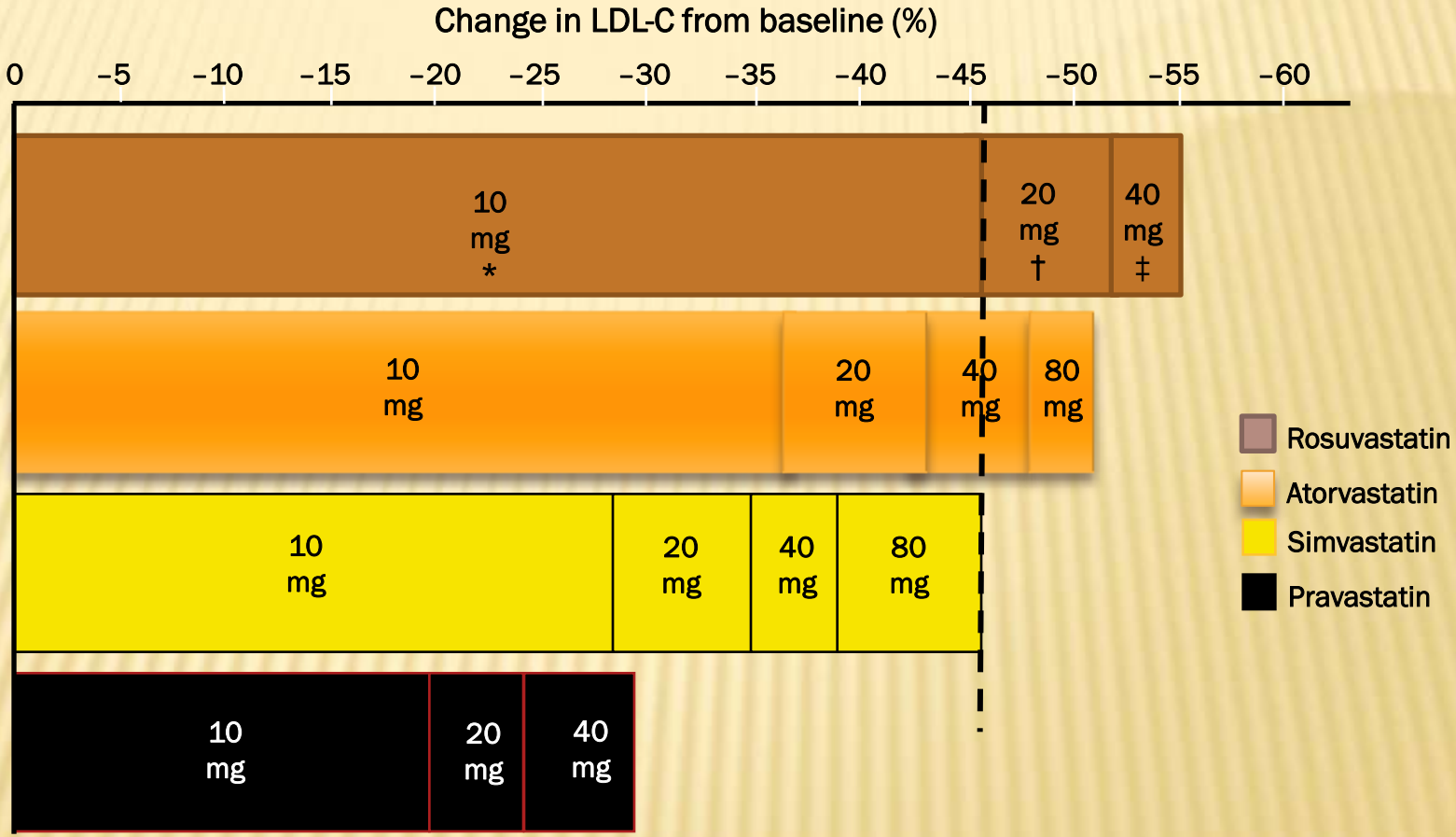

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‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

Adapted from Jones P et al. *Am J Cardiol* 2003; 92: 152–160


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PRIMARY PREVENTION

Patients with Diabetes and LDL-C 70-189 mg/dL (age 40-75 years) without clinical ASCVD

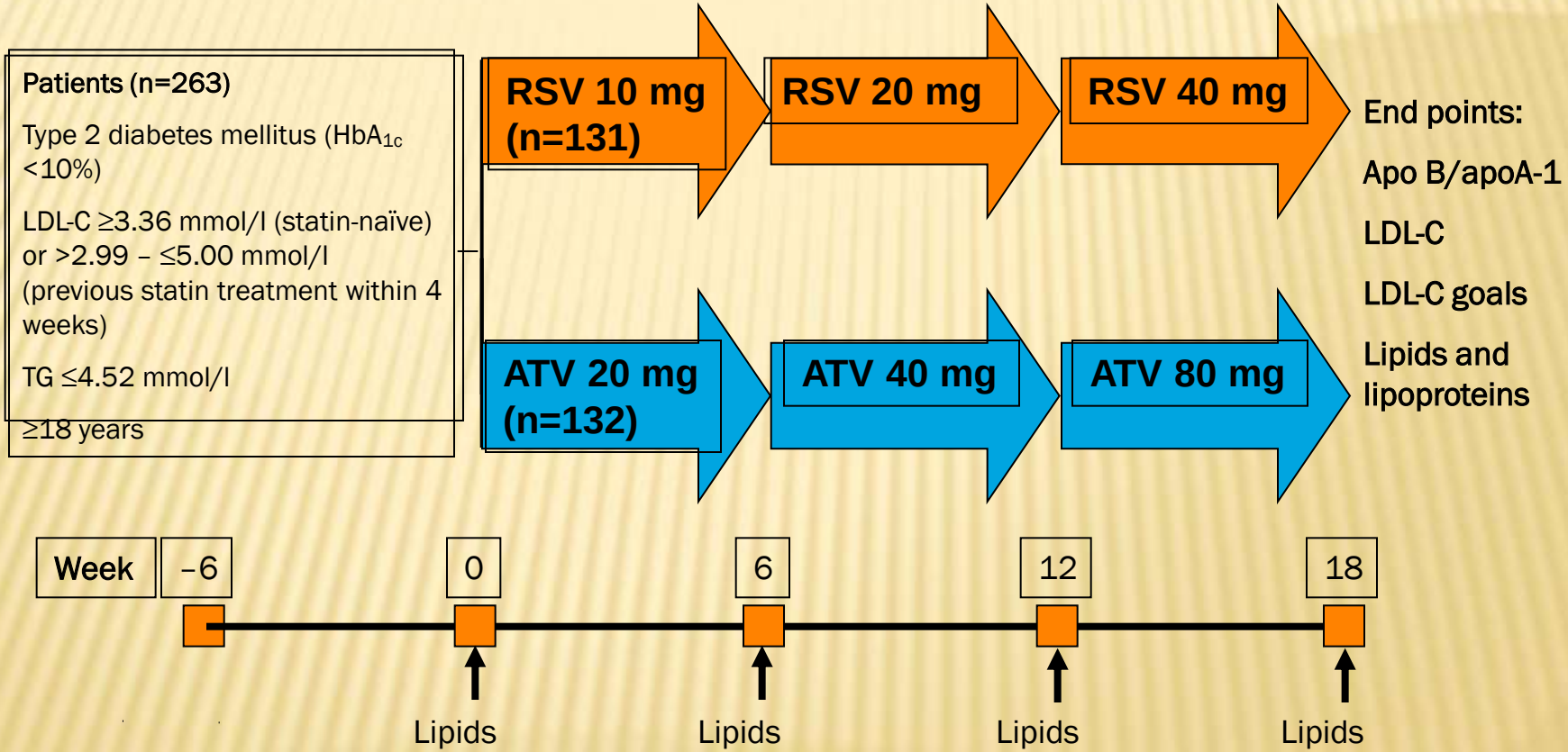
→ Moderate-Intensity Statin

→ High-Intensity Statin if ≥7.5% estimated 10-year ASCVD risk*

* Estimated using Pooled Cohort Risk Assessment Equations

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

CORALL
Study design

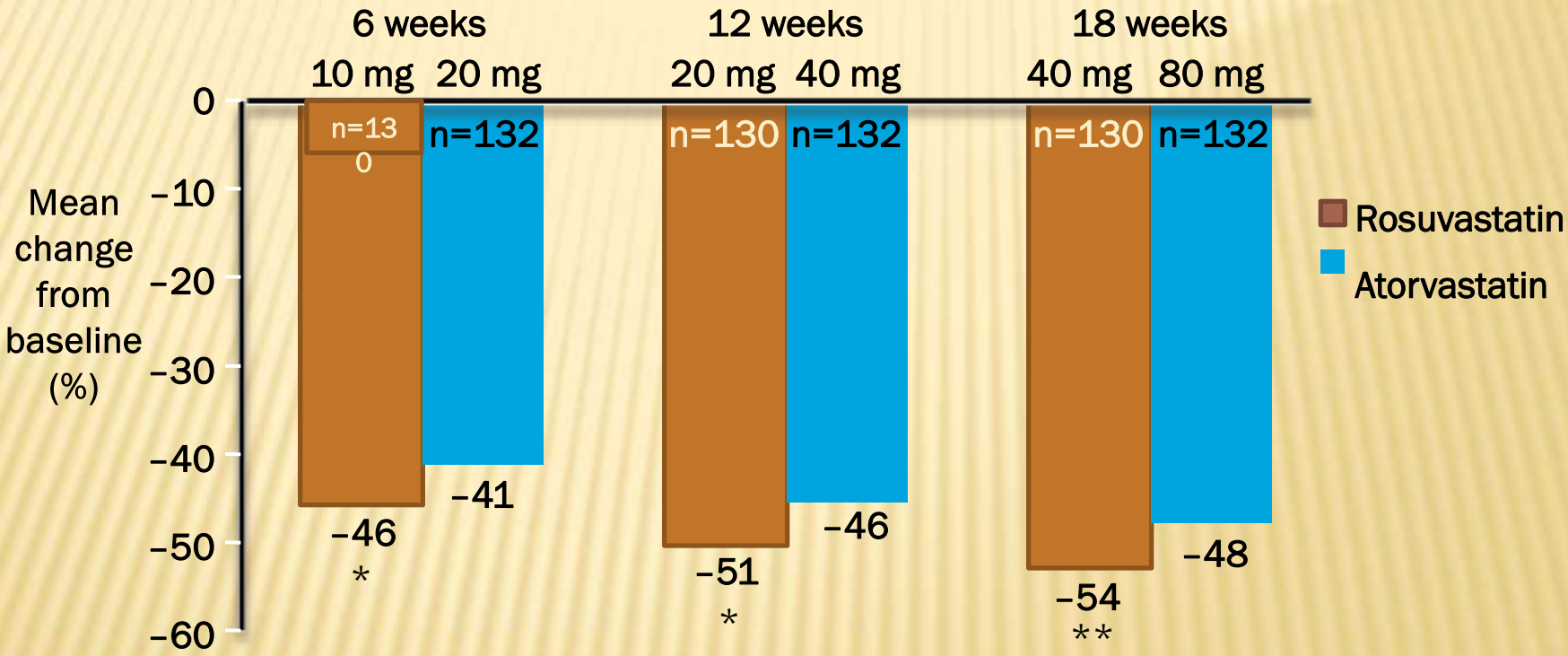


RSV=rosuvastatin; ATV=atorvastatin

Franken et al. *Atheroscler Suppl* 2004; 5: 118

CHANGE IN LDL-C WITH ROSUVASTATIN AND ATORVASTATIN IN HIGH-RISK PATIENTS

THE CORALL STUDY

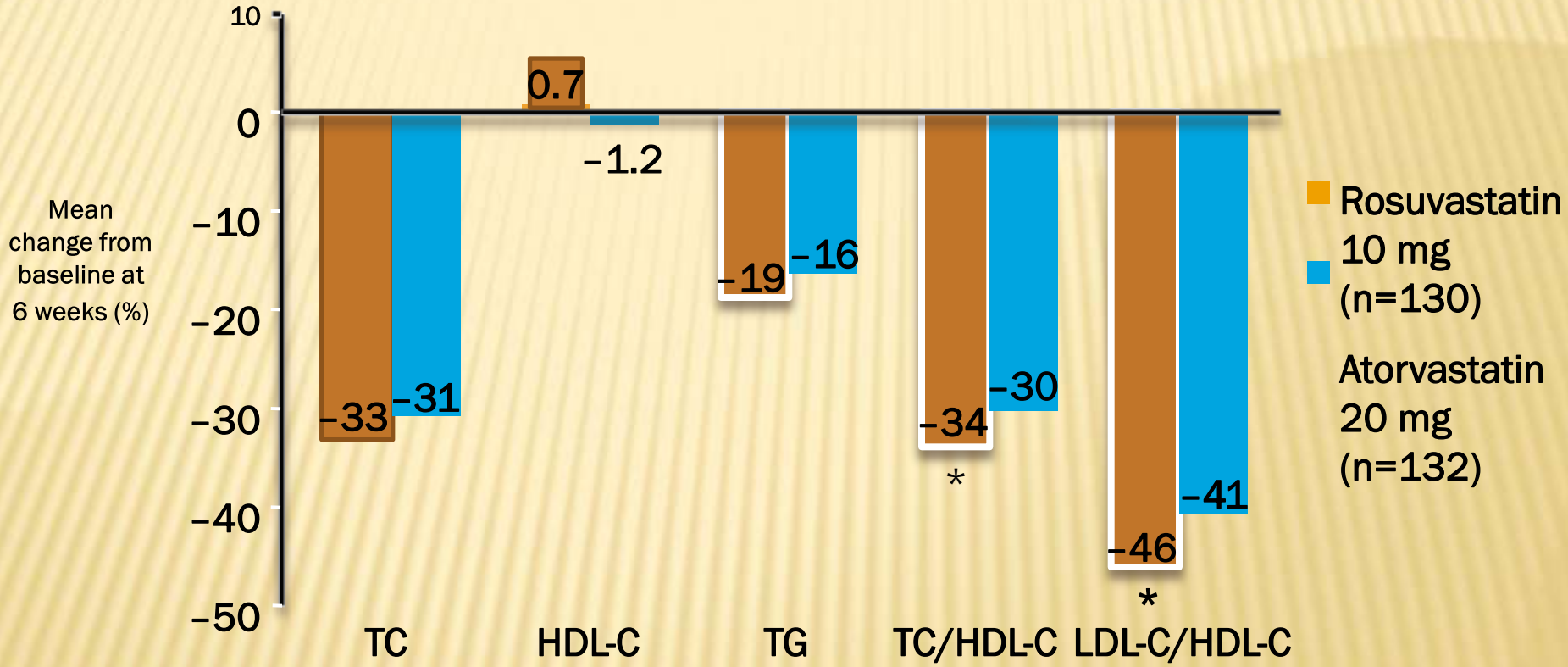


*p<0.05vs ATV, **p<0.01 vs ATV

Wolffenbuttel BHR et al. *J Int Med* 2005; 257: 531–539

CHANGE IN LIPID PROFILE WITH ROSUVASTATIN AND ATORVASTATIN IN HIGH-RISK PATIENTS

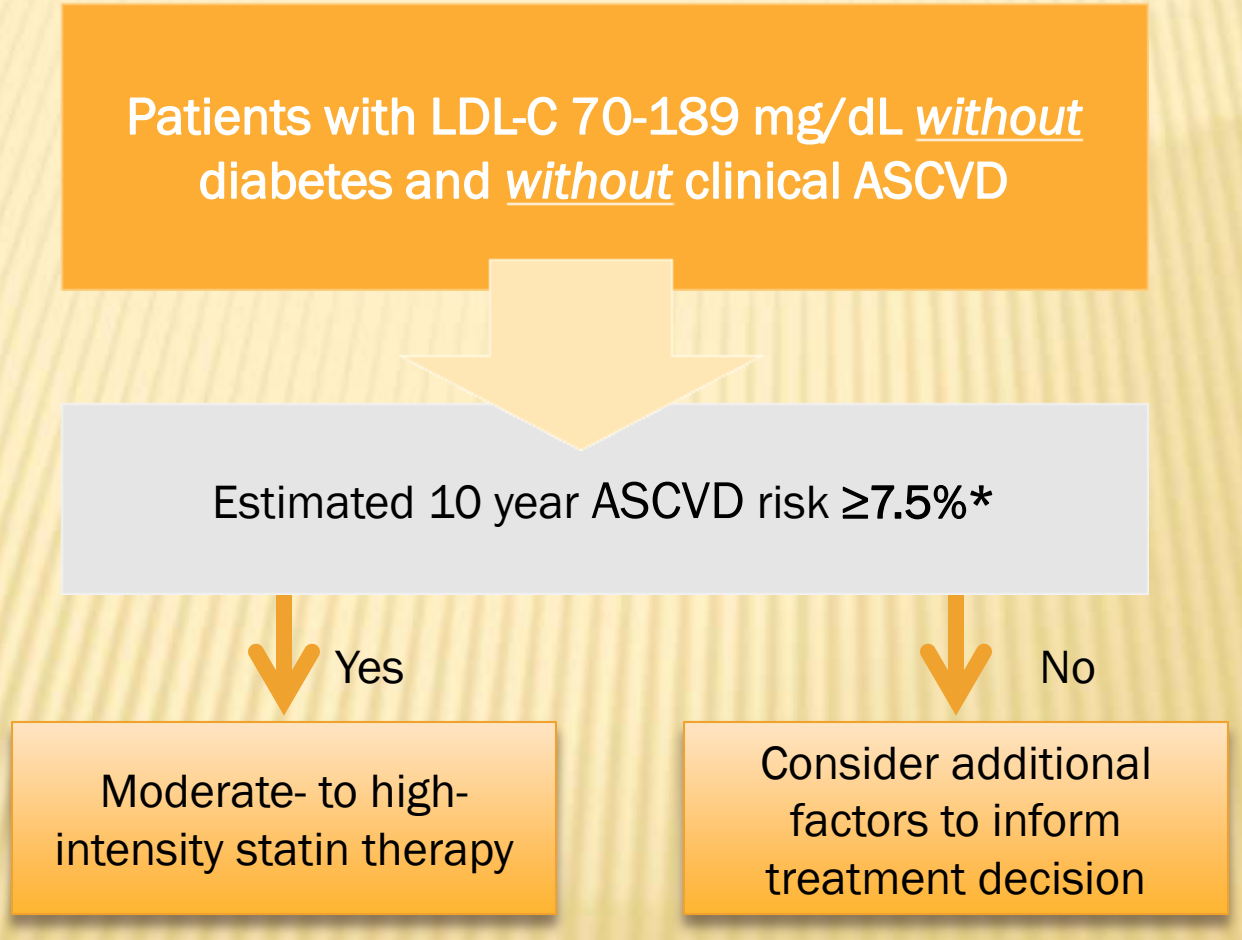
THE CORALL STUDY



*p<0.05 vs ATV 20 mg

Wolffenbuttel BHR et al. *J Int Med* 2005; 257: 531–539

PRIMARY PREVENTION



* Estimated using the Pooled Cohort Risk Assessment Equations

Stone NJ, et al. *J Am Coll Cardiol.* 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

ROLE OF BIOMARKERS AND NON-INVASIVE TESTS IN ASSESSING ASCVD RISK

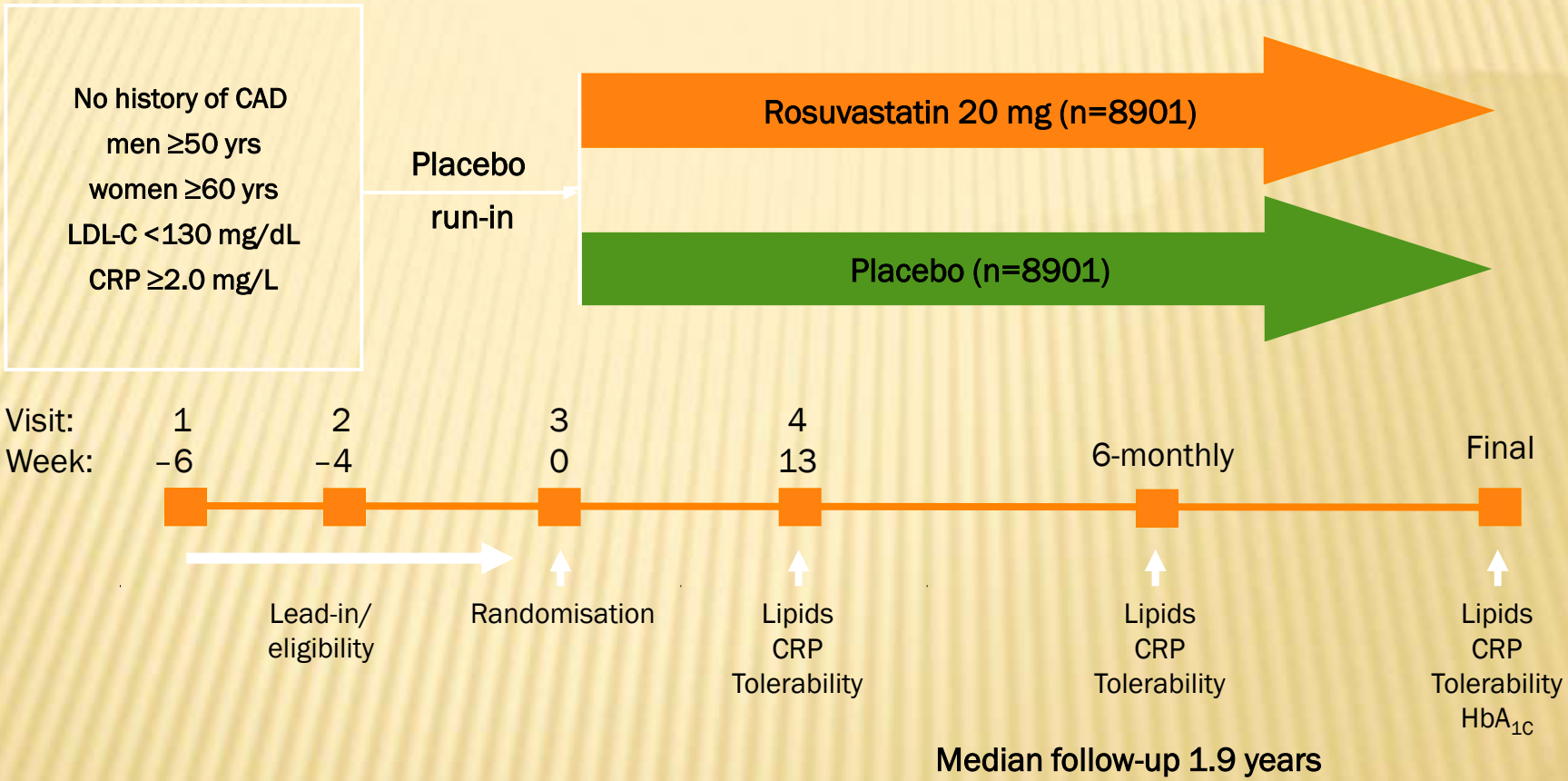
Treatment decisions in selected individuals who are *not included* in the 4 statin benefit groups may be informed by other factors as recommended by the Risk Assessment Work Group guideline

Factors include:

- Primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias
- Family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative
- High-sensitivity C-reactive protein ≥2 mg/L
- Coronary Artery Calcium score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity
- Ankle-brachial index <0.9
- Elevated lifetime risk of ASCVD

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

JUPITER – STUDY DESIGN



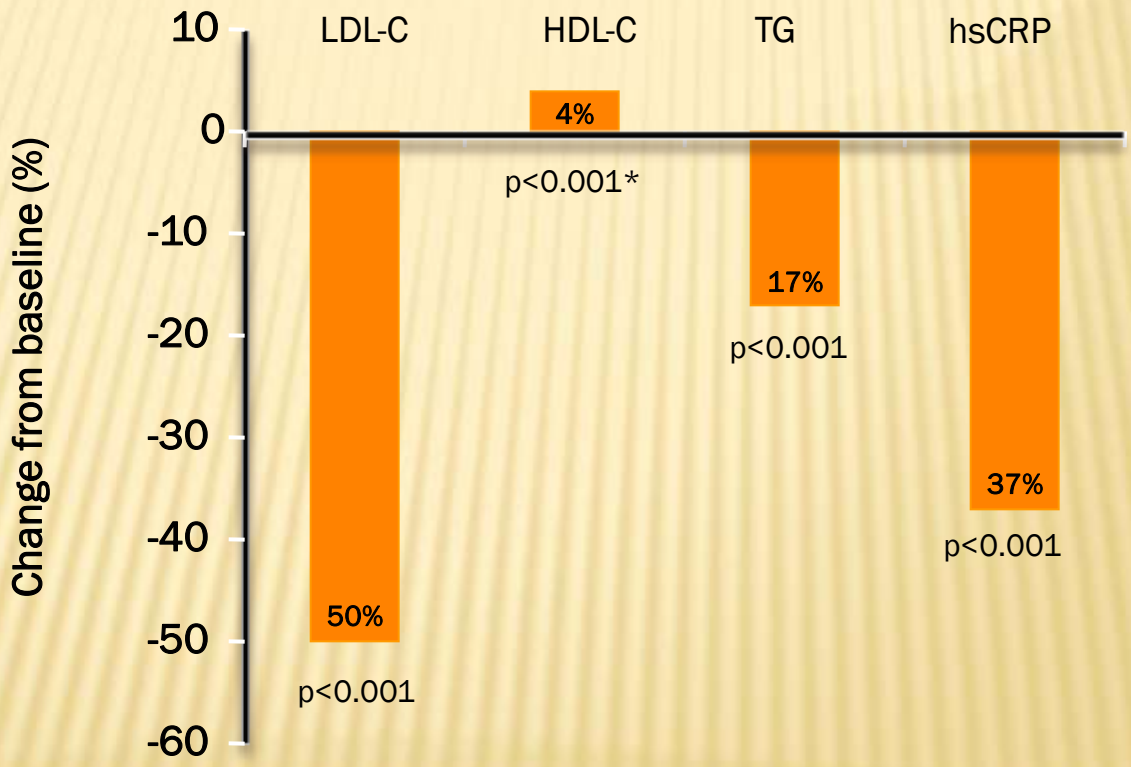
CAD=coronary artery disease; LDL-C=low-density lipoprotein cholesterol; CRP=C-reactive protein; HbA_{1c}=glycated haemoglobin

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER

EFFECTS ON LDL-C, HDL-C, TG AND HSCRP AT 12 MONTHS;

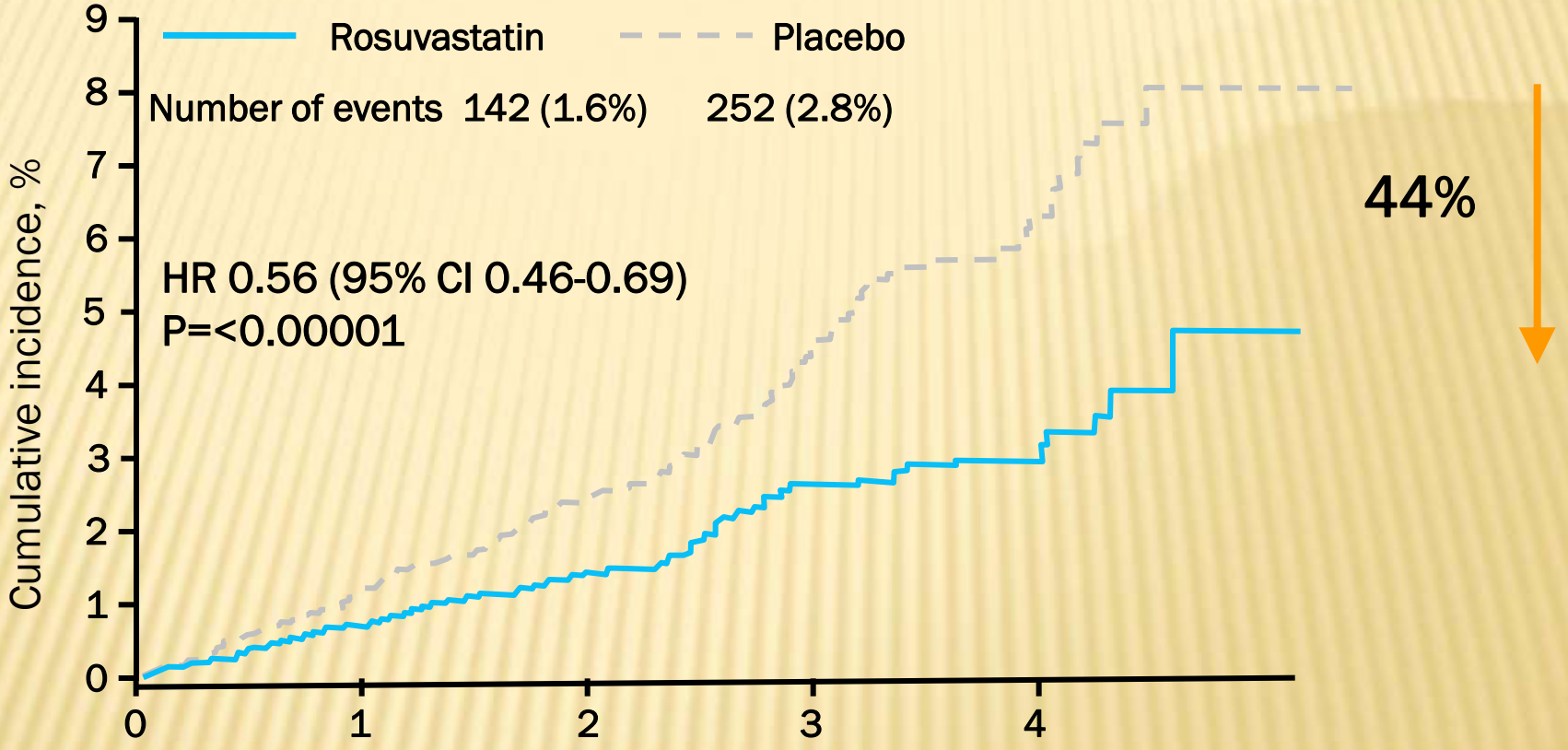
PERCENTAGE CHANGE BETWEEN ROSUVASTATIN AND PLACEBO



*P-value at study completion (48 months) = 0.34

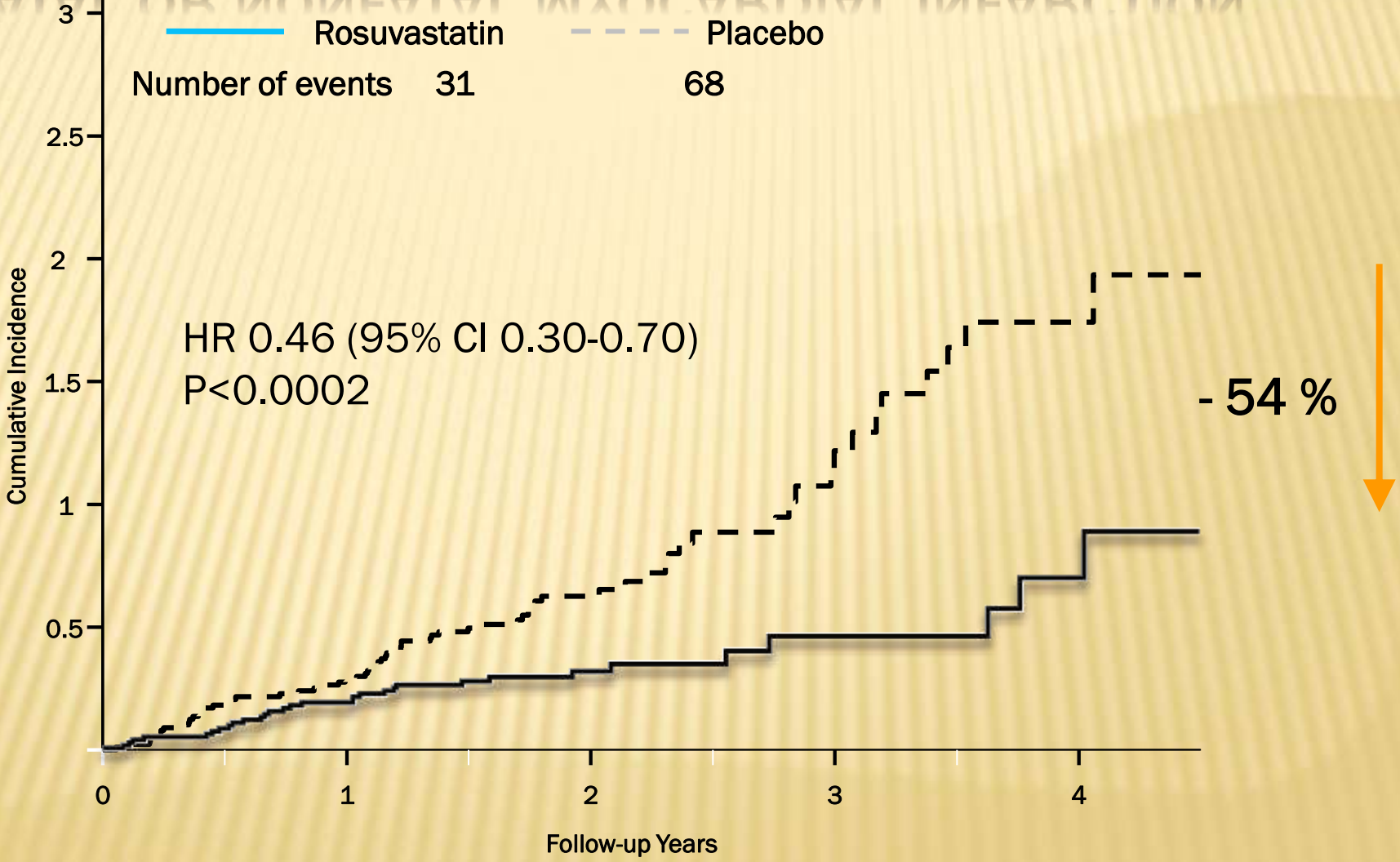
Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER: PRIMARY ENDPOINT

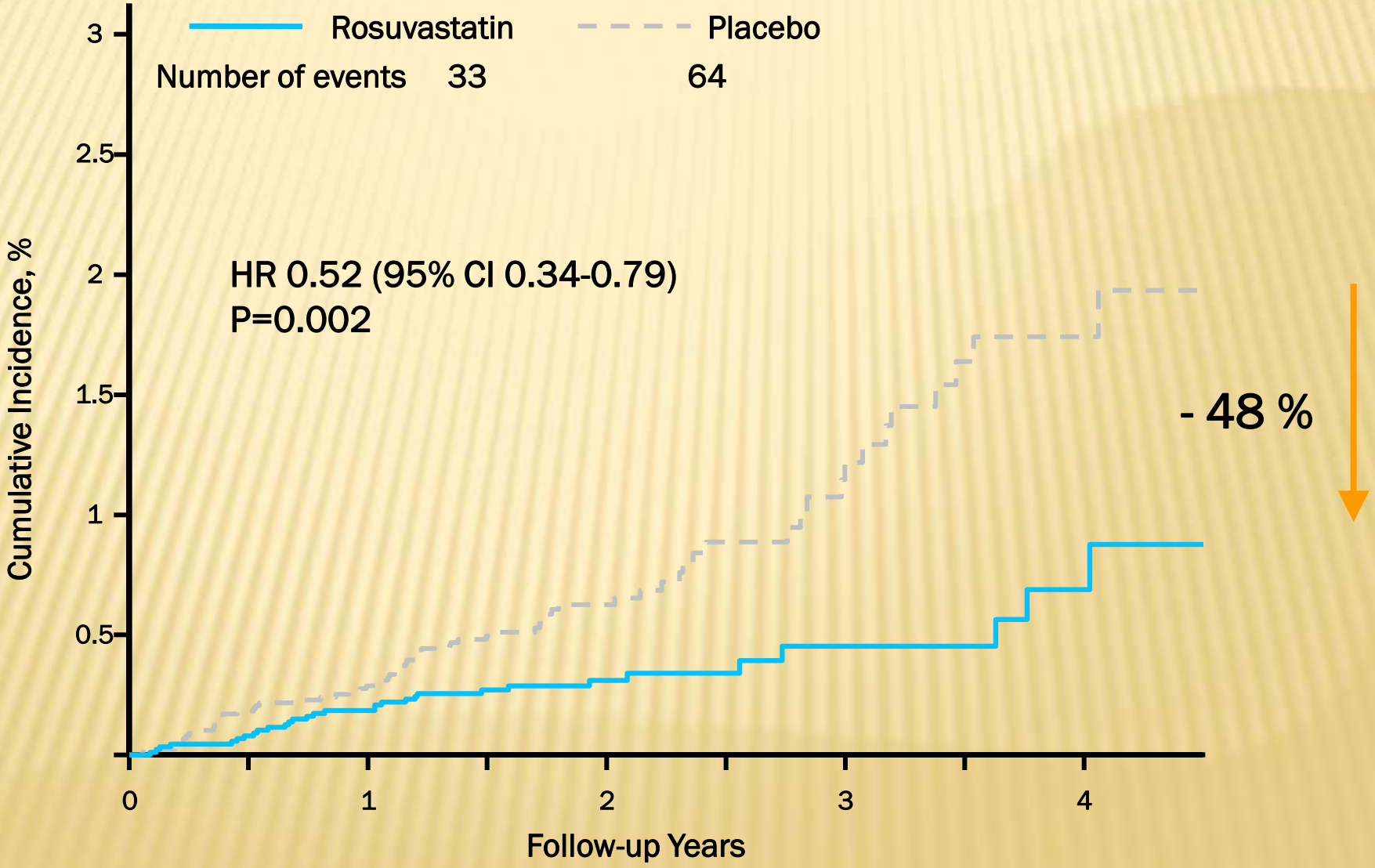


Number at risk						
Rosuvastatin	8901	8412	3892	1352	543	156
Placebo	8901	8353	3872	1333	534	173

JUPITER:
FATAL OR NONFATAL MYOCARDIAL INFARCTION



JUPITER: FATAL OR NONFATAL STROKE




N.B.

A NEW PERSPECTIVE ON LDL–C AND/OR NON-HDL–C TREATMENT GOALS

Lack of RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets

No recommendations for or against specific LDL-C and non-HDL-C goals for primary or secondary prevention

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

RECOMMENDATIONS FOR NON-STATIN THERAPIES

- No data supporting the routine use of non-statin drugs combined with statin therapy to further decrease ASCVD events

- In high-risk patients who have an insufficient response to statin therapy, or who are unable to tolerate either a statin or the recommended statin intensity, addition of a non-statin cholesterol-lowering therapy can be considered

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

SUMMARY: 2013 GUIDELINE RECOMMENDATIONS FOR STATIN THERAPY

ASCVD Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention

Clinical ASCVD	LDL-C ≥190 mg/dL	Diabetes;age 40-75 years*	Estimated 10-yr ASCVD risk ≥7.5%†; age 40-75 years*
• High-Intensity statin (age ≤75 years) • Moderate-intensity statin if >75 years or not a candidate for high-intensity statin	• High-intensity statin • Moderate-intensity statin if not a candidate for high-intensity statin	• Moderate-intensity statin • High-intensity statin if estimated 10 year ASCVD risk ≥7.5%	• Moderate- to high-intensity statin

ASCVD prevention benefit of statin therapy may be less clear in other groups . Consider additional factors influencing ASCVD risk , potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.

* With LDL-C of 70-189 mg/dL

† Estimated using the Pooled Cohort Risk Assessment Equations

Stone NJ, et al. J Am Coll Cardiol. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

SAFETY CONSIDERATIONS

Selection of appropriate statin

- Select the appropriate statin and dose based on patient characteristics, level of ASCVD* risk, and potential for adverse effects
- Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present
- Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
  - Multiple or serious comorbidities, including impaired renal or hepatic function
  - History of previous statin intolerance or muscle disorders
  - Unexplained ALT elevations >3 times ULN
  - Patient characteristics or concomitant use of drugs affecting statin metabolism
  - >75 years of age
- Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:
  - History of hemorrhagic stroke
  - Asian ancestry
- Statins used in combination with other cholesterol-lowering drug therapies might require more intensive monitoring

*Based on the presence of clinical ASCVD, diabetes mellitus, LDL-C ≥190 mg/dL, or level of estimated 10-year ASCVD risk

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

CASE 1

62 year old AA male

Total cholesterol: **140 mg/dl** ×

Low HDL: **35 mg/dl** ×

SBP: **130 mmHg** ×

Not taking anti-hypertensive medications. ×

Non-diabetic. ×

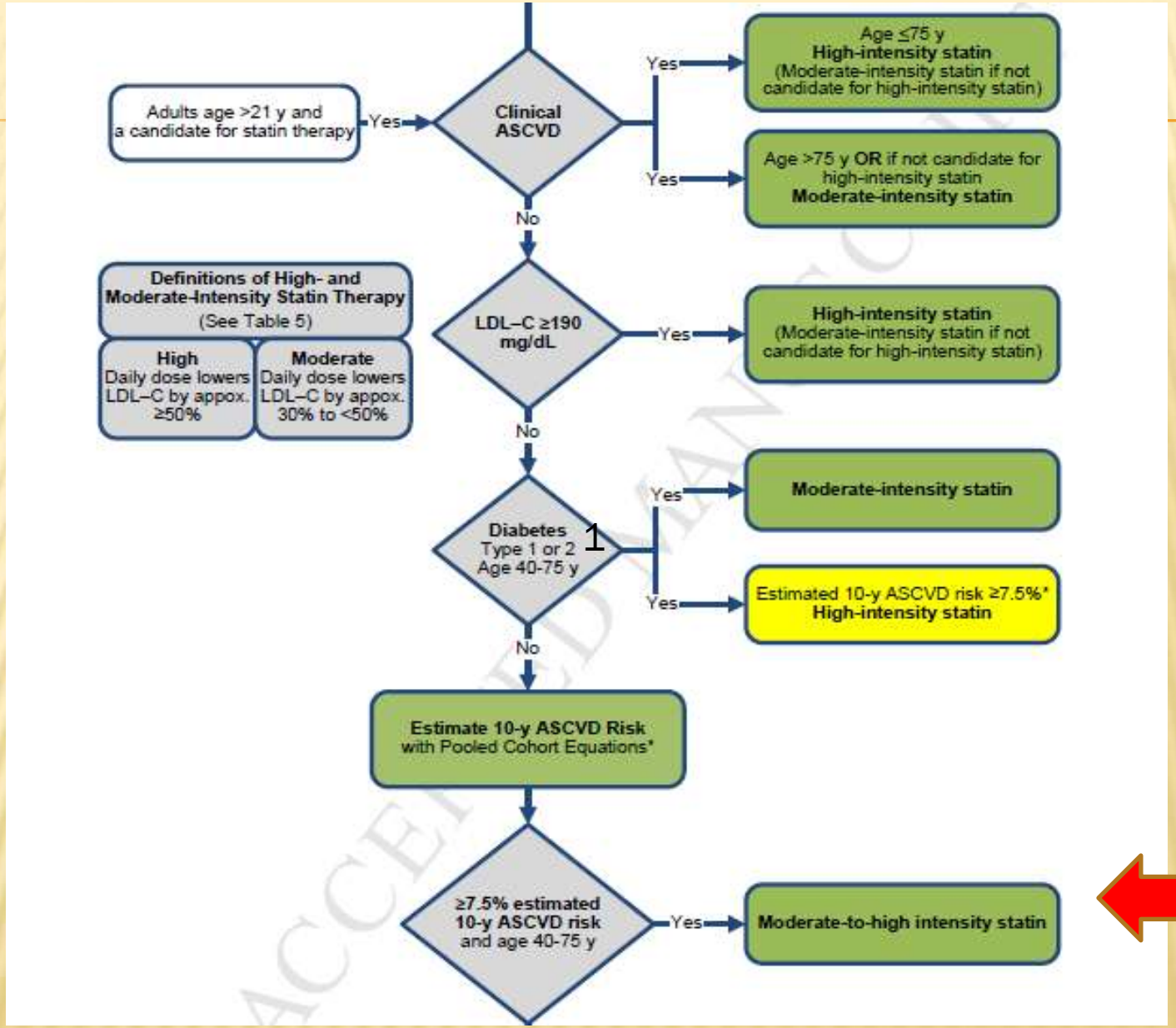
Non-smoker. ×

Calculated 10 yr risk of ASCVD : **9.1%** ×

QUESTION

- What do you think is the best statin group for this patient?

- Statin isn't recommended.
- low – Intensity.
- Moderate to high Intensity.


Adults age >21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)
High
Daily dose lowers LDL–C by appox. ≥50%
Moderate
Daily dose lowers LDL–C by appox. 30% to <50%
LDL–C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Diabetes
Type 1 or 2
Age 40-75 y
1
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated 10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin

INTENSITY OF STATIN THERAPY

High-Intensity Statin Therapy	Moderate-Intensity Stain Therapy	Low-Intensity Statin Therapy
LDL–C ↓ ≥50%	LDL–C ↓ 30% to <50%	LDL–C ↓ <30%
Atorvastatin (40†)–80 mg Rosuvastatin 20 *(40)* mg	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Lifestyle modification remains a critical component of ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies.

Statins/doses that were not tested in randomized controlled trials (RCTs) reviewed are listed in *italics*
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL
‡Initiation of or titration to simvastatin 80 mg not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

CASE 2

50 year old white female

Total cholesterol : 180 mg/dl ×

HDL: 50 mg/dl ×

SBP: 130 mmHg ×

taking anti-HTN medication ×

+diabetic ×

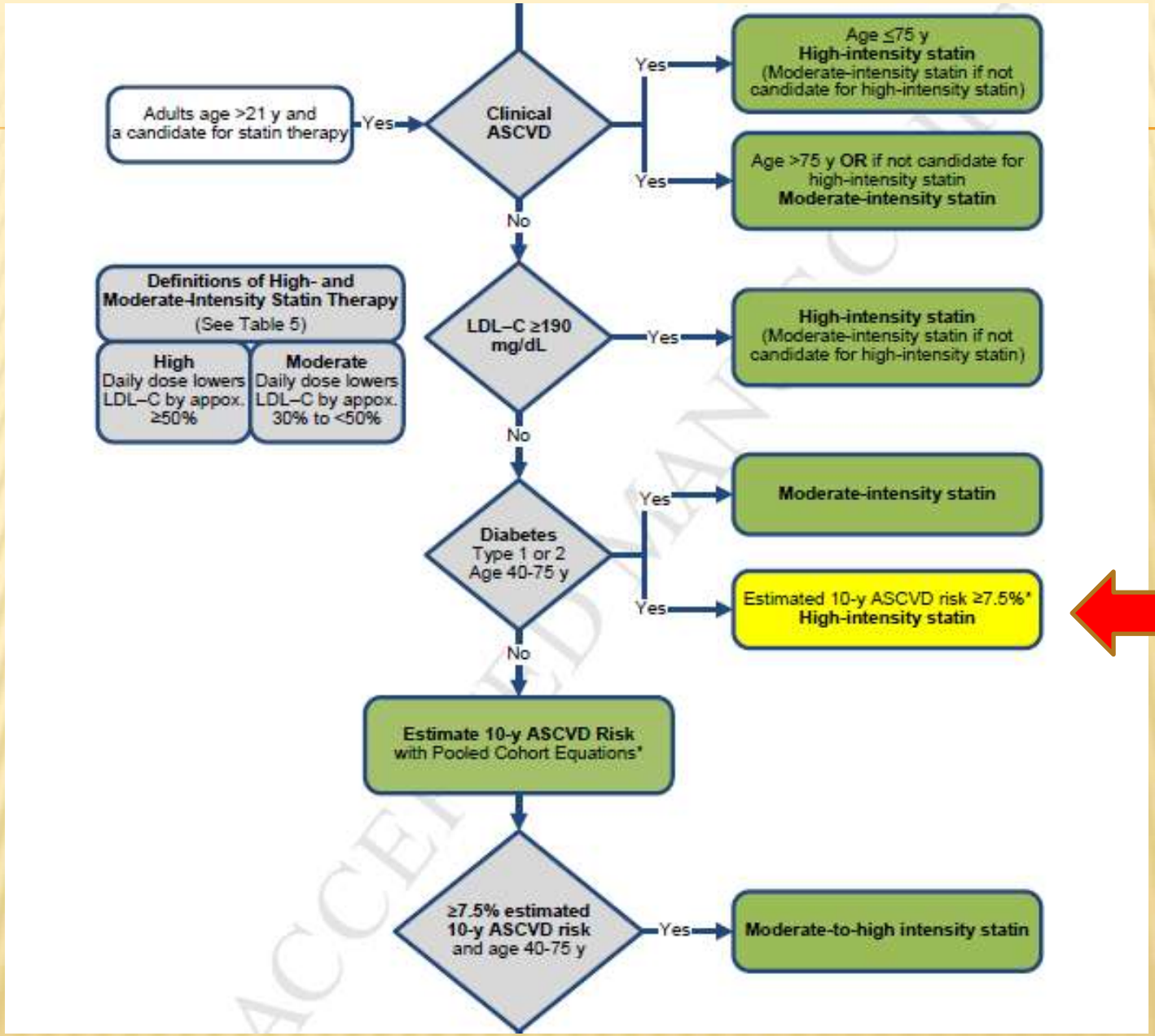
+smoker ×

Calculated 10 yr ASCVD: 9.8% ×

QUESTION

- What do you think is the best statin group for this patient?

  - High – Intensity.
  - Moderate – Intensity.
  - low Intensity.
  - None of the above.


Adults age >21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)
High
Daily dose lowers LDL–C by appox. ≥50%
Moderate
Daily dose lowers LDL–C by appox. 30% to <50%
LDL–C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Diabetes
Type 1 or 2
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated 10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin

INTENSITY OF STATIN THERAPY

High-Intensity Statin Therapy	Moderate-Intensity Stain Therapy	Low-Intensity Statin Therapy
LDL–C ↓ ≥50%	LDL–C ↓ 30% to <50%	LDL–C ↓ <30%
Atorvastatin (40†)–80 mg Rosuvastatin 20 *(40)* mg	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Lifestyle modification remains a critical component of ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies.

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Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

CASE 3

48 year white female

Total cholesterol : **180 mg/dl** ×

HDL: **55 mg/dl** ×

SBP: **130 mmhg** ×

Not taking anti-HTN medications ×

Diabetic ×

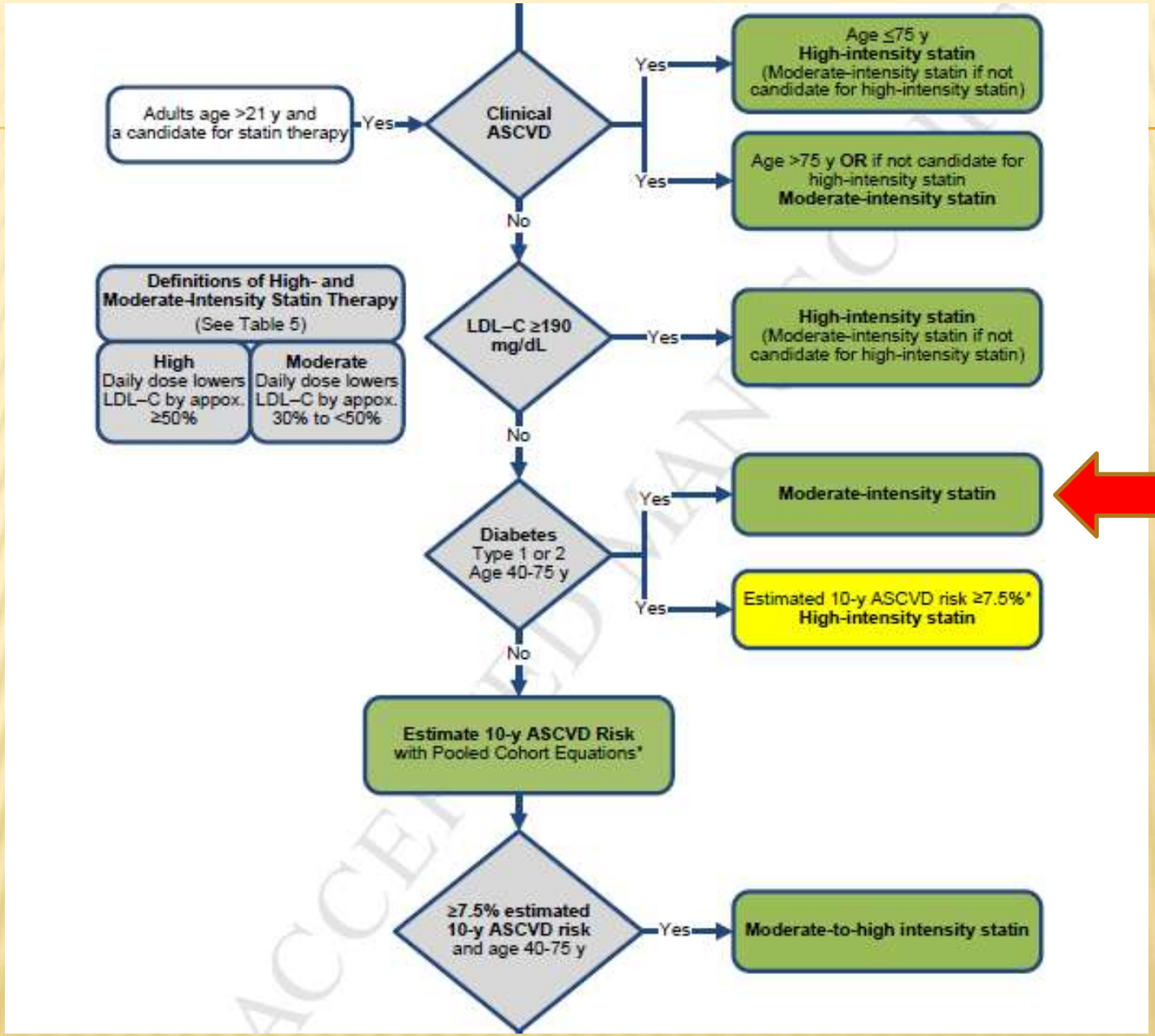
Non-smoker ×

Calculated 10 year risk ASCVD : **1.8%** ×

QUESTION

- What do you think is the best statin group for this patient?

  - High – Intensity.
  - Moderate – Intensity.
  - low Intensity.
  - None of the above.


Adults age >21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)
High
Daily dose lowers LDL–C by appox. ≥50%
Moderate
Daily dose lowers LDL–C by appox. 30% to <50%
LDL–C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Diabetes
Type 1 or 2
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated 10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin

INTENSITY OF STATIN THERAPY

High-Intensity Statin Therapy	Moderate-Intensity Stain Therapy	Low-Intensity Statin Therapy
LDL–C ↓ ≥50%	LDL–C ↓ 30% to <50%	LDL–C ↓ <30%
Atorvastatin (40†)–80 mg Rosuvastatin 20 *(40)* mg	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

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Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

CASE 4

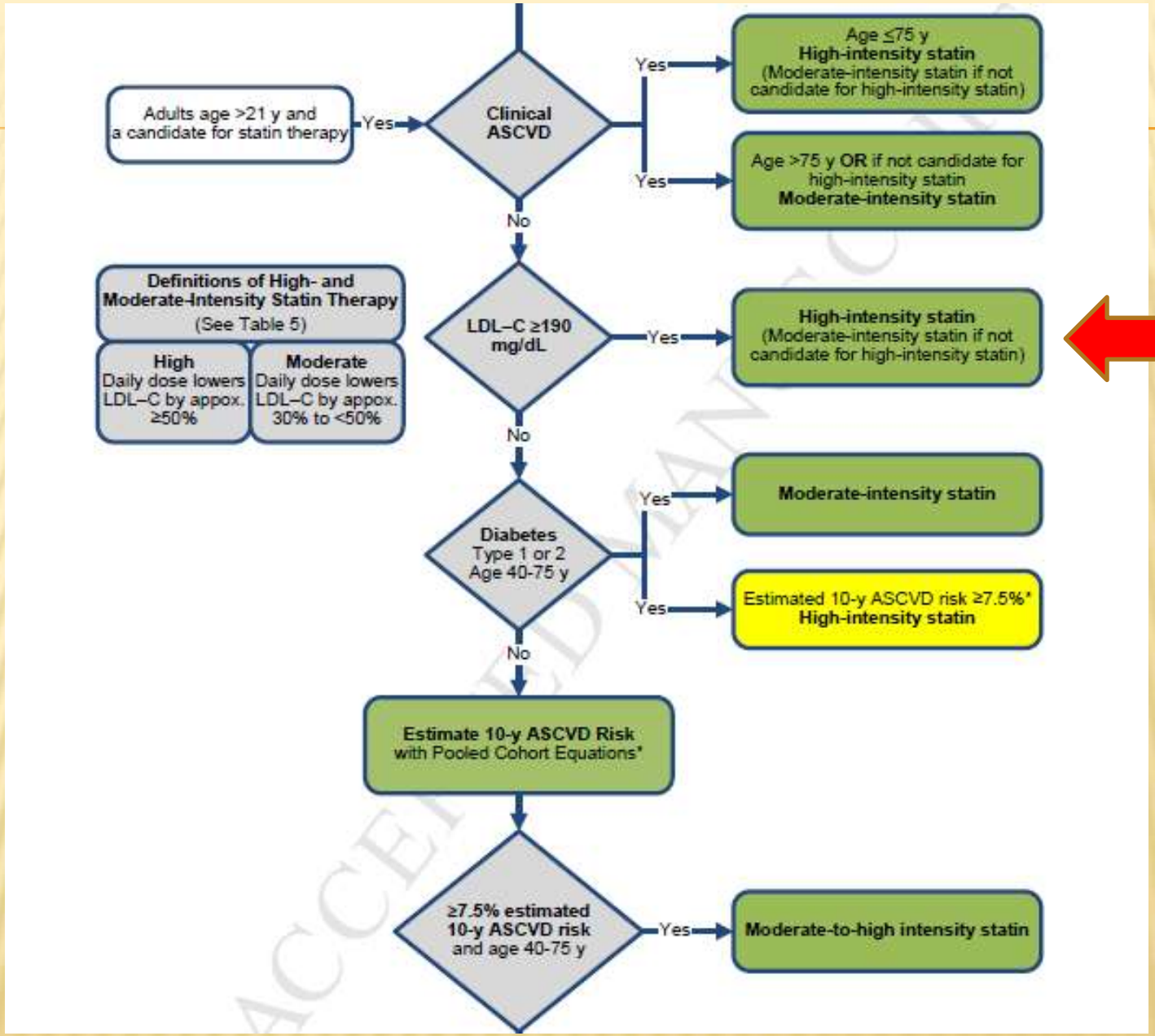
22 year white male

- LDL-C: 195 mg/dl ✖
- SBP: 120 mmhg ✖
- Not taking anti-HTN meds ✖
- Non-diabetic ✖
- Non-smoker ✖

QUESTION

- What do you think is the best statin group for this patient?

  - High – Intensity.
  - Moderate – Intensity.
  - low Intensity.
  - None of the above.


Adults age >21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
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(See Table 5)
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Moderate
Daily dose lowers LDL–C by appox. 30% to <50%
LDL–C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Diabetes
Type 1 or 2
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated 10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin

CASE 5

66 yr white female

High Total cholesterol: **230 mg/dl** ×

HDL: **55 mg/dl** ×

SBP: **150 mmhg** ×

taking anti-HTN meds ×

Non-diabetic ×

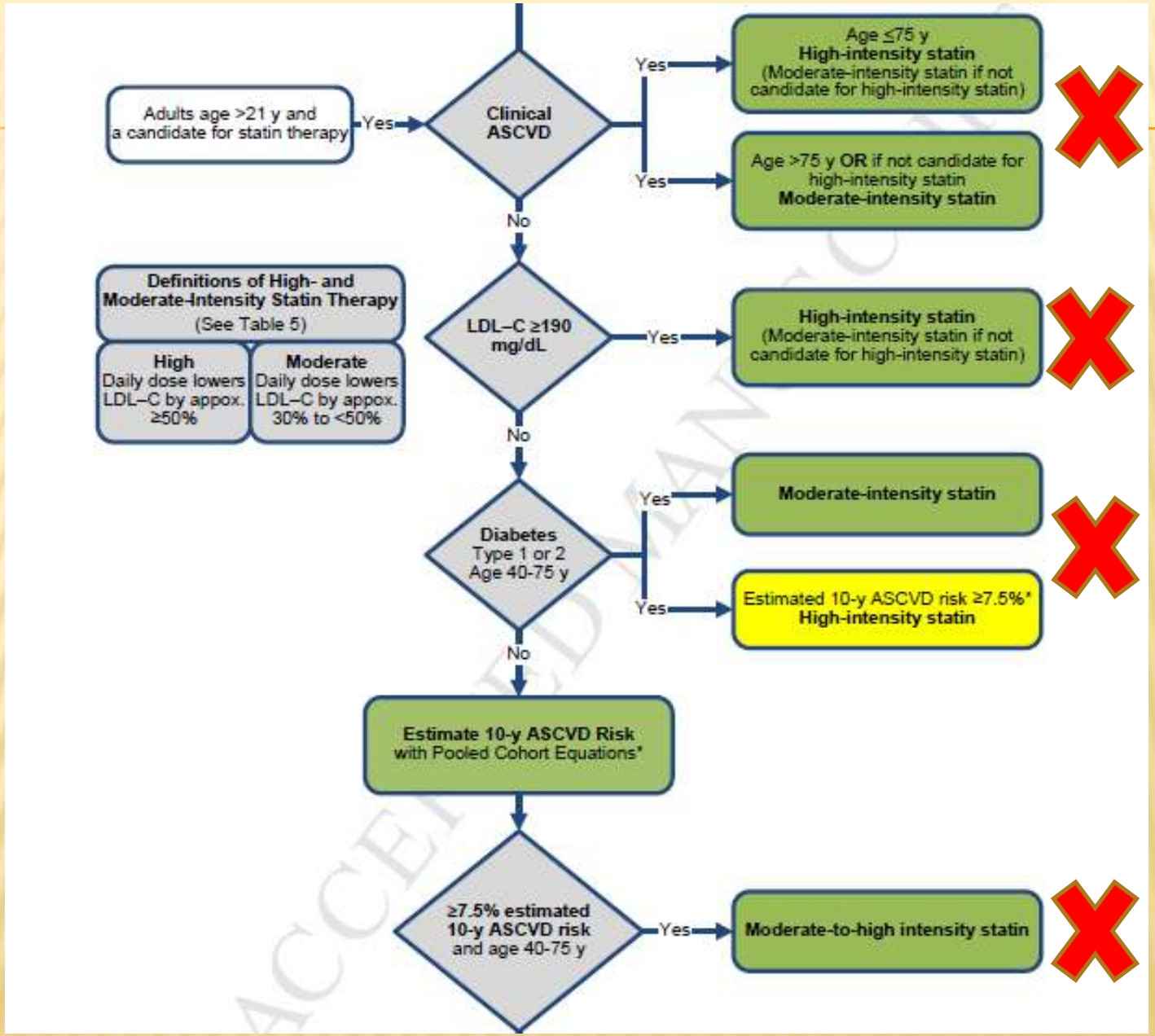
Non-smoker ×

Calculated 10 yr risk of ASCVD : **2.0 %** ×

QUESTION

- What do you think is the best Statin group for this patient?

  - Moderate – Intensity.
  - High – Intensity.
  - Moderate to high Intensity.
  - None of the above.


Adults age >21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)
High
Daily dose lowers LDL–C by appox. ≥50%
Moderate
Daily dose lowers LDL–C by appox. 30% to <50%
LDL–C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Diabetes
Type 1 or 2
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated 10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin

Statin therapy NOT recommended unless there are other factors to be considered

WHAT IS NEW IN THE 2013 GUIDELINE?

- Identification of 4 major statin benefit groups
- Shift away from treat to target approach
- Definitions of statin intensity provided
- New global risk assessment tool for primary prevention
- Addition of non-statin drug therapy to statins to further decrease ASCVD risk addressed

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

SUMMARY

- 4 major statin benefit groups identified for whom ASCVD risk reduction outweighs the risk of adverse events
- Shift away from a treat to target LDL-C approach
- No longer recommend non-statin drug therapy in combination with statins to further decrease ASCVD events

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LAST MESSAGE

- 4 major statin benefit groups identified for whom ASCVD risk reduction outweighs the risk of adverse events
- Shift away from a treat to target LDL-C approach
- No longer recommend non-statin drug therapy in combination with statins to further decrease ASCVD events

Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.


Thank You